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STUDIES UPON THE LIFE CYCLES OF THE BACTERIA.

Part I.

REVIEW OF THE LITERATURE, 1838-1918.

BY

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CONTENTS.

STUDIES UPON THE LIFE CYCLES OF THE BACTERIA.

INTRODUCTION.

Results obtained in comparative studies upon the morphology and the life history of some important soil bacteria, especially of those of the Azotobacter group, made it advisable to extend these investigations, so that representatives of other prominent groups of bacteria were also included. Short reports of these investigations have been made in two preliminary communications (*Löhnis* and *Smith*, 1916 *a* and *b*), wherein it was pointed out that undoubtedly the complete life history of all bacteria is much more complicated than has been generally assumed. Our findings were summarized in the first paper (l. c., p. 700) as follows:

> All bacteria studied live alternately in an organized and in an amorphous stage. The latter has been called the "symplastic" stage, because at this time the living matter, previously inclosed in the separate cells, undergoes a thorough mixing either by a complete disintegration of cell wall, as well as cell content, or by a "melting together" of the contents of many cells which leave their empty cell walls behind them. In the first case a readily stainable, in the latter case an unstainable "symplasm" is produced.
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> According to the different formation and quality of the symplasm the development of new individual cells from this stage follows various lines. In all cases at first "regenerative units" become visible. These increase in size, turning into "regenerative bodies," which later, either by germination or by stretching, become cells of normal shape. In some cases the regenerative bodies also return temporarily into the symplastic stage.
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> Besides the formation of the symplasm, another mode of interaction between the plasmatic substances in bacteria cells has been observed, consisting of the direct union of two or more individual cells. This "conjunction" seems to be of no less general occurrence than the process first mentioned. Its physiological significance remains to be studied.
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> All bacteria multiply not only by fission but also by the formation of "gonidia"; these usually become first regenerative bodies, or occasionally exospores. Sometimes the gonidia grow directly to full-sized cells. They, too, can enter the symplastic stage. The gonidia are either liberated by a partial or a complete dissolution of the cell wall, or they develop while still united with their mother cell. In the latter case the cell wall either remains intact or it is pierced by the growing gonidia, which become either buds or branches.
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> Some of the gonidia are filterable. They also produce new bacteria either directly or after having entered the symplastic stage.
>
> The life cycle of each species of bacteria studied is composed of several subcycles showing wide morphological and physiological differences. They are connected with each other by the symplastic stage. Direct changes from one subcycle into another occur, but they are rather rare exceptions. The transformation of spore-free into spore-forming bacteria seems to be dependent on the conditions acting upon the symplasm and regenerative bodies.

The fact that all the different phases in the life history of the bacteria, i. e., conjunction, formation and development of regenerative bodies, symplastic stage, and the occurrence of different subcycles with peculiar cell morphology, were to be recorded constantly and regularly in all cases studied by us, made the conclusion inevitable that these apparently new facts must have been observed in the course of many previous investigations, though they usually have not attracted much attention, and hardly any of the bacteriological textbooks furnishes information upon them. The practical aims of most of the bacteriological investigations, together with the widespread adherence to standardized methods and theories, have been distinctly unfavorable to thorough studies along such lines. Nevertheless, at least a few references could be given in our preliminary communications, and it was to be expected that a systematic search of the literature would lead to the rediscovery of more confirmative reports, which so far had not found any acknowledgement, or which have been rejected on account of their being not in agreement with the prevalent theory. This expectation has been fully verified.

At the present time it is out of the question to make a complete collection of all such details, which are widely scattered in a gigantic literature. When in 1875 *Ferdinand Cohn* pub-

lished the second part of his "Untersuchungen über Bacterien" he was of the opinion that the literature even at that time was so voluminous that a complete survey were hardly possible even for the specialist. In 1880 *Prazmowski* made a similar remark when he reported on his "Untersuchungen über die Entwicklungsgeschichte und Fermentwirkung einiger Bakterien." Since then, every year has added thousands of new bacteriological publications. It would be an inexcusable waste of time to study all of them again in the light of the newly discovered facts. But I earnestly hope that in the discussion of the literature, as presented on the following pages, no important contribution has been overlooked, so that the general situation is presented with fair accuracy, and all those authors have been mentioned who have tried to shed more light upon the life history of the bacteria.

Complete reports upon our own experimental investigations will be given later. For making a proper arrangement of this review of the literature, however, our two preliminary communications, published in 1916, will be used. As will be seen from the following pages, every phase in the life history of the bacteria has been observed by several, sometimes even by many, independent workers, though only in comparatively few cases the complete life cycle of a distinct species has been discovered.

It seems best to arrange the whole matter in the following five chapters:

I. Different cell forms.
II. Reproductive organs. (Gonidia. Regenerative bodies. Spores. Microcysts.)
III. Formation of the symplasm and regeneration of cells.
IV. Conjunction.
V. Methods.

In chapters I and II a considerable number of details concerning the different groups of bacteria will have to be discussed. For this purpose, and in accordance with the general standpoint taken at present by most bacteriologists, the following five groups of organisms may be accepted:

(*a*) Cocci.
(*b*) Nonspore-forming rods.
(*c*) Spore-forming rods.
(*d*) Spirilla and spirochaets.
(*e*) Higher bacteria (trichobacteria, mycobacteria).

As will be seen later, this arrangement is not in accordance with the true character of and the natural relations existing among the bacteria. But as long as these facts and relations are not more completely known, it will be best to adhere to that more familiar grouping. At the end of Chapters I, II, and III some conclusions will be drawn from the observations reviewed therein, which might be helpful for further investigations. For the same reason the methods have been treated separately in Chapter V.

It is hardly necessary to point out that the data collected from the literature are of very different value, and we are often left in doubt as to their correct interpretation. Much of the material discussed on the following pages is awaiting further critical experimental study.

Special attention has been given to the morphological side of the subject. Unquestionably the physiological side is of equal or even greater importance. However, as the situation is at present, with most bacteriologists on the one side adhering to the dogma of simplicity and constancy of the form of the bacteria, while on the other side admitting a more or less considerable variability in their physiological behavior, it appears to be of prominent importance that in the first place a more correct knowledge of the morphological basis of bacteriology will be secured. As soon as the morphology of the different phases in the life cycles of the bacteria will have received adequate treatment, physiological investigations will also furnish much more satisfactory results than are obtainable now. And only after the full life history of the different types of bacteria will have been studied it will become possible to define their natural relations and to come ultimately to a correct systematic arrangement of the various species, genera, and families of the bacteria.

I. DIFFERENT CELL FORMS.

1. GENERAL DISCUSSION.

It would be preferable, if the different forms of the vegetative cells alone could be treated in this chapter, leaving to Chapter II all details concerning formation, appearance, and development of the various reproductive organs (gonidia, regenerative bodies, and spores); but this is not possible at the present time. In many cases, of course, a distinct separation is quite feasible; sometimes, however, we are left more or less in doubt whether the forms mentioned in the literature are those of vegetative or of reproductive cells. This holds true especially for many of the globular bodies. The reproductive organs, which we call gonidia and regenerative bodies, have been frequently considered to be micrococci, a mistake which indeed is quite excusable. Both of them are able to multiply as such, and as this fact is more easily to be observed than their germination, usually their real character has not been discovered. On the other hand, it does not infrequently happen that typical micrococci almost imperceptibly change from the vegetative into the reproductive state by thickening their cell wall and assuming the character of cysts, which fact, however, can be discovered only by a very close study. Other cells, too, may display either vegetative or reproductive activities without undergoing conspicuous changes in their appearance, so that their correct classification may also cause some difficulties. But even if all reproductive cells could be as clearly distinguished and separated from the vegetative cells, as is the case with the endospores, still a considerable number of trustworthy observations would remain, proving beyond doubt that, if not all, undoubtedly very many bacteria have shown themselves to be able to appear in different forms, while in the vegetative state.

(a) MONOMORPHISTIC AND PLEOMORPHISTIC THEORIES.

The questions concerning monomorphism or pleomorphism of the bacteria have been extensively treated by European as well as by American authors during several decades. The new point of view, which is furnished by the fact that the bacteria, like other microörganisms, exhibit different forms and activities in the various stages of their life cycles, makes it necessary to review briefly the opinions promulgated in this respect, for at least some of them may eventually become of considerable value in future researches.

In the French literature pleomorphistic ideas have been always en vogue. At first, before the theory of spontaneous generation was fought by *Pasteur*, the transformation of the "globules élémentaires," found in the residues of plant and animal life, into "infusoires" was the main point of discussion. The writings of *Dujardin* (1841), *Pineau* (1845), *Pouchet* (1863), *Trécul* (1865–1867), and *Béchamp* (1883) are to be mentioned especially in this respect. *Robin* (1871, p. 931) was inclined to consider all micrococci, bacteria, and vibriones simply as stages in the development of his *Leptothrix buccalis*. *Davaine* (1876), however, correctly emphasized, as had been already done by *Dujardin*, that undoubtedly many different species exist; bacterium and vibrio are declared to be related to Leptothrix, but not to be identical with it. When studying a distinct species, it is said to be of special importance to pay attention to the variability of its forms "qui changent suivant diverses conditions." *Duclaux* (1883) wrote in his "Chimie biologique" (p. 33):

> En résumé, toute classification fondée sur des caractères purement morphologiques semble impossible . . . Pour donner une idée de l'incertitude qui en resulte, je dirai que la qualification de Bacillus subtilis a été donnée déjà a une dizaine d'êtres, tous identiques si on ne consulte que leur nom, tous différents si on ne consulte que les propriétés qui leur sont attribuées dans les divers mémoires qui en parlent.

The following statement, made by *Artigalas* (1885, p. 23), forecasts our present standpoint with remarkable accuracy:

Nous verrons qu'un microbe donné peut, à une certaine période de son évolution, être rapporté à un type dont il se sépare complètement dans la suite. En un môt, un microbe peut passer par des transformations telles que, comparé à lui-même, l'expérimentation seule en puisse démontrer l'identité.

Correcting an erroneous view and tendency, which was rather common at that time and later in the German as well as in the American literature, *Guignard* and *Charrin* wrote, reporting on their interesting experiments "Sur les variations morphologiques des microbes" (1887):

Ce polymorphisme . . . n'ébranle en rien la notion généralement admise pour l'espèce; il n'en doit pas moins attirer de plus en plus l'attention sur l'influence des milieux . . . et mettre en garde contre certaines tendances à trop multiplier les espèces en se fondant sur des données morphologiques, insuffisantes.

More evidence against the assumed constancy of form and function was furnished by *Wasserzug's* publications (1888 *a* and *b*). *Metchnikoff*, too, in various contributions (1889–1894), dwelt upon the "pléomorphisme, si répandu dans le monde des bactéries."

In the third edition (1890) of "Les bactéries et leur rôle dans l'étiologie, l'anatomie et l'histologie pathologique des maladies infectieuses" *Cornil* and *Babes* defined their standpoint as follows (Vol. I, pp. 18 and 30):

Un grand nombre de botanistes affirment que les bactéries présentent des formes diverses suivant le degré de leur développement et le milieu nutritif où elles sont placées. Cette polymorphie est bien démontrée pour un grand nombre d'entre elles . . . On doit même se demander si toutes les bactéries ne présentent pas des formes variées et si l'on ne décrit pas aujourd'hui un même microbe sous plusieurs noms différents.—Il ne faudrait pas croire que les formes des bactéries soient toujours constantes, immuables, de façon à caractériser des genres distincts. Tout au contraire, on sait que certains micro-organismes revêtent des formes diverses pendant leur développement de telle sorte qu'ils se présentent comme un coccus, un bâtonnet, un filament ou une spirale dans les états successifs de leur accroissement.

Similar to *Artigalas*, *Billet* (1890) emphasizes the necessity of investigating the complete life-history of the bacteria, because, as he says (p. 217):

On reconnaîtra peut-être alors qu'un grand nombre des formes que l'on décrites jusqu'ici comme des espèces absolument distinctes étrangères l'une à l'autre, ne sont, en réalité, que des formes d'éléments appartenant à la même espèce.

When *Rodet* in 1894 published his book entitled "La variabilité dans les microbes," *Arloing*, who wrote the preface for it, made the following reference to the dogmatism of *R. Koch* and his pupils:

Il fut un temps où l'on croyait qu'un microbe avait des fonctions immuables comme sa forme . . . Les microbes étaient donc specifiquement et rigoureusement determinés par la forme et les propriétés. Cela était un dogme sur lequel semblait reposer toute la microbie. Un novateur ne pouvait le menacer sans soulever des protestations ou faire naître un sentiment de défiance a l'égard de ses travaux.

Further proof supporting the pleomorphistic view was also furnished by *Arloing* himself in cooperation with *Chantre* (1894).

Macé (1897) is the only French author who has sometimes been quoted as standing on the monomorphistic side. He is, indeed, of the opinion that much of what has been found by other French bacteriologists in their investigations upon the variability of the bacteria has been obtained under special, distinctly abnormal conditions (p. 13). But he also writes, very similar to *Cornil* and *Babes*, concerning the one-sided theory held at that time by most of the German bacteriologists (p. 12):

Cette opinion a été fortement battue en brèche, lorsqu'on est arrivé à prouver que certaines espèces pouvaient, selon les circonstances de milieu ou la phase de leur cycle évolutif, donner tantôt des cellules sphériques, des Coccus, tantôt des bâtonnets courts, tantôts des filaments droits, tantôt des filaments spirales.

The same more or less pleomorphistic standpoint is also taken in the more recent French publications, e. g., in the textbooks of *Miquel* and *Cambier* (1902), *Burnet* (1911), who even says (p. 66): "Les bactéries sont variables au point de dérouter les bactériologistes;" *Le Blaye* and *Guggenheim* (1914), and *Kayser* (1914). The latter once more clearly emphasizes the point which in the German, as well as in the American, literature has caused much misunderstanding (p. 28):

Cette grande variété de formes n'est nullement en contradiction avec l'unité de l'espèce.

In the British bacteriological literature the pleomorphistic point of view is not quite so generally accepted as was the case in France. *Huxley* (1870), who unfortunately believed in the accuracy of the work done by *Hallier* and *Lüders* in Germany, thought that really Penicillium could produce Torula and this bacteria, a hypothesis which was at once refuted by *Burdon-Sanderson* (1871). *Bastian*, on the other hand, became a persistent advocate (1872–1914) of the theory of heterogenesis as it was upheld by the earlier French writers (*Pineau, Pouchet, Trécul, Béchamp*). Distinctly pleomorphistic ideas were also promoted by *Lister* (1873) and by *Lankester* (1873–1876). *Lister* himself modified his statements later (1878) as far as they were based on incorrect conclusions drawn from results obtained with mixed cultures. But he was right when he said (1873) that a classification of the bacteria based upon absolute morphological constancy "is entirely untrustworthy;" and his clear drawings of branching and budding bacteria also deserve our interest to-day. *Lankester*, too, undoubtedly worked with impure cultures, but it must not be overlooked that much of his work is based on continuous microscopic observations of the changes in morphology exhibited by his *Bacterium rubescens*. And at least in some cases it still can be shown, as will be done in Chapter III, that in fact his observations have been much more accurate than those of his critics.

A distinctly monomorphistic standpoint was taken by *E. Klein* (1885) in his textbook on "Microörganisms and Disease," obviously under German influence. He points out that true micrococci never elongate to form rods, and mentions as such "true micrococci" *F. Cohn's* "*Micrococcus*" *prodigiosus* and *violaceus*, which he also found to be always globular and immotile, contrary to now well-known facts. But his own observations on anthrax, cholera, and other pathogenic organisms equally militated against his standpoint. And some years later, after he had found that *Bacillus anthracis* sometimes assumes a morphological character which resembles very much that of some Saccharomyces or Oidium, he even did not hesitate to say (1894): "Probably it returns to an atavistic stage in its evolutional history."

H. M. Ward (1887) clearly states that "Schizomycetes are pleomorphic," but, as he adds, this is "no reason to deny the existence of distinct species." *Woodhead* (1891), on the other hand, is of the opinion that the doctrine of pleomorphism "can not be accepted as in any way proved except in the case of a few well-known nonpathogenic forms," whereas, according to *Crookshank* (1896, p. 478), this doctrine is "widely accepted" and—

Researches by competent observers have more recently clearly demonstrated that several microörganisms in their life cycle exhibit successfully the shapes characteristic to the orders of Cohn. . . These facts obviously shake the very foundation of *Cohn's* classification, and we are left without possessing a sound basis for classification into genera and species.

Hewlett (1902) writes that "a certain amount of pleomorphism undoubtedly occurs in some organisms," and *Muir* and *Ritchie* (1903) equally admit that "there are cases where evidence appears to exist of the occurrence of pleomorphism."

Harris (1893) found that one of two aerobic organisms isolated from oedema was able to exhibit "a complete series from cocci to bacilli." The other, too, was "remarkable for its pleomorphism." *Durham* (1898) studied closely the dimorphism of Micrococcus melitensis. *Adami* (1892–1899) furnished other important contributions concerning the variability of the bacteria. Together with *M. E. Abbott* and *Nicholson* (1899) he was able to show that especially *B. coli* may grow as a minute coccus, which also differs entirely in its cultural character from the typical form. Another report upon these investigations, to which we have to refer later, was published by *M. E. Abbott* (1900).

Dobell (1911, p. 484) believes "that the greater number of bacteria are pleomorphic," and he continues:

The bacteria are in no way a group of simple organisms, but rather a group displaying a high degree of morphological differentiation coupled in many cases with a life cycle of considerable complexity.

Revis (1912 *a*) changed a Coli strain experimentally to such an extent "that it now was neither physiologically, morphologically nor culturally a Colon bacillus." *Rowland* (1912) succeeded in imposing all marks of *B. pseudotuberculosis rodentium* upon a typical strain of *B. pestis*. And results secured with many kinds of organisms, led *Young* (1914) to the hypothesis

"that all bacteria formed merely stages in the life history of a group of organisms with an extremely complicated life cycle."

The most important contributions to our subject, however, in modern British literature are those of *Hort* (1915–1917) and his collaborators, to which we will have to refer frequently. It was with good reason that *Adami* (1916), after having become acquainted with these new observations, raised the question:

> Have we all these decades been wrong in our faith, that bacteria are the simplest of all living forms of life, possessed of asexual multiplication by fission only? May there not be intercalated other phases in the life history of the schizomycetes?

The German and Austrian bacteriological literature shows an interesting change from monomorphistic to extremely pleomorphistic views, then back to the rigorously monomorphistic standpoint of *R. Koch* and his pupils, and at last an almost general acceptance of the moderate pleomorphism as it has always been taught by French bacteriologists.

Although there is no special discussion upon this problem, the monomorphistic point of view is already clearly discernible in *Ehrenberg's* (1838) as well as in *F. Cohn's* (1853) early publications. It is, however, by no means, that strict monomorphism which was advocated 20 years later by the same author. *Bact. termo*, e. g., was declared to be able to grow in globular, curved, or rodlike form.

The extreme pleomorphism, on the other hand, promulgated especially by *Hallier* (1865–1878) and by *Lüders* (1866), undoubtedly was not supported by sufficiently reliable observations, but it can also not be considered fair to condemn summarily all what has been written by *Hallier* as being "scientific nonsense" (*Winter*, p. 33), or as merely belonging to the scientific "chronique scandaleuse" (*DeBary*, p. 137). As much of this work was based on long continued direct microscopic studies, some of his results, though obtained with impure cultures, still retain their value, and will even regain new interest in connection with other data which are to be discussed in Chapter II. The same holds true in respect to various facts observed by *Karsten* (1869). This author, as well as *H. Hoffmann*, already in 1869 and with good reason rejected *Hallier's* erroneous assumption of a direct connection existing between fungi and bacteria. *Hoffmann's* publication is of special interest, because it contains the first drawings of branched bacteria, which later were rejected by the extreme monomorphists.

Morphological changes of single bacteria cells have been studied directly under the microscope by *Rindfleisch* (1872), as well as by *Billroth* (1874). The latter author has been repeatedly called the champion of the older pleomorphism, usually on account of no other reason than that he named all bacteria together *Coccobacteria septica*. But he left it explicitly (p. 35) for the botanists to decide, whether or not the different forms which he observed were merely different types of growth of this one *Coccobacteria septica* or whether several genera and species should be made.

It is a similar case with *Nägeli's* standpoint. Usually the following sentence (1877, p. 20) has been quoted as convincing proof of his alleged error:

> Ich habe seit zehn Jahren wohl tausende von verschiedenen Spaltpilzformen untersucht, und ich könnte (wenn ich Sarcina ausschliesse) nicht behaupten, dass auch nur zur Trennung in zwei specifisch verschiedene Formen Nöthigung vorhanden sei.

However, the following statement in the same publication (1877, p. 22) also must be taken under consideration:

> Wenn ich sage, dass die uns bekannten morphologischen Eigenschaften der Spaltpilze und ihr Vermögen, verschiedene Zersetzungen zu bewirken, eine generische und specifische Unterscheidung nicht rechtfertigen, und dass selbst die Möglichkeit vorliege, alle Formen in eine einzige Species zu vereinigen, so liegt es mir doch fern, diese Behauptung wirklich auszusprechen. In einer Sache, in welcher die morphologische Beobachtung und der physiologische Versuch den Forscher noch so sehr im Stiche lassen, ist es überhaupt gewagt, eine bestimmte Ansicht auszusprechen.

In his later work (1882, p. 130) he defends himself against those who assert that he be inclined to consider all bacteria one species. But at the same time he points out that also according to his new experiments with pure cultures, all morphological and physiological qualities of

the bacteria may vary to a considerable extent. His standpoint is best defined by the following quotation (p. 138):

Es wird bei den Spaltpilzformen die nämliche Erfahrung sich wiederholen, die in neuerer Zeit an den übrigen Pilzen gemacht wurde, wo die verschiedenartigsten morphologischen und physiologischen Erscheinungen als verschiedene Generationen einer und derselben Species erkannt wurden. Die Species wird nicht durch absolute Merkmale kenntlich sein, sondern dadurch, dass sie unter bestimmten äusseren Umständen bestimmte Modificationen des morphologischen und physiologischen Verhaltens, unter anderen Umständen andere Modificationen zeigt. Ein System der Spaltpilze nach Gattungen und Arten mit den jetzigen Hilfsmitteln aufzustellen hat keinen wissenschaftlichen Wert.

That, in fact, bacilli may assume sometimes distinctly coccoid shape, and spirilla may temporarily look like straight rods, *Nägeli* was able to ascertain with pure cultures. Some years earlier *Klebs* (1875 *b*) had made a similar statement, also based on direct microscopic observations.

When *Ferdinand Cohn* began the publication of his "Untersuchungen über Bacterien" (1872), he also, by no means, advocated those extreme monomorphistic ideas, which later, mostly on account of the writings of his followers, have been attributed to him. He strongly emphasized that genera, as well as species, proposed by him were to be considered form genera and form species, not natural ones. The following lines (1872 *b*, p. 130) clearly define his original standpoint:

Wir sind genötigt, bei den Bacterien in vielen Fällen ein Verfahren anzuwenden, das auch in der Mycologie so lange festgehalten wird, als nicht durch vervollkommnete Culturmethoden die gesamte Entwicklungsgeschichte der Arten festgestellt werden kann. . . . Es besteht darin, dass jede Form, die sich durch hervorstechende Merkmale auszeichnet, mit einem besonderen Gattungsnamen belegt wird; jede kleinere Abweichung wird als Species unterschieden. Es soll damit nicht die Möglichkeit ausgeschlossen werden, dass nicht verschiedene solcher Species aus einer und derselben Mutterform hervorgehen, ja dass nicht selbst verschiedene Gattungen nur Entwicklungszustände eines und desselben Individuums sein können.

In his later contributions (1875, p. 142; 1876, p. 274) *Cohn* changed his mind in so far as he now declared his genera to be natural, not only form genera. His own investigations, however, did not support this statement. There was indeed no possibility at that time to study the complete life history of these smallest organisms, and *Cohn's* classification is clearly incorrect in many cases. E. g., he mentions in his "natural" genus Micrococcus, which is said (1872 *b*, p. 151) to be made up of immotile globular or oval cells, the following species:

Micr. prodigiosus, luteus, aurantiacus, chlorinus, cyaneus, violaceus, ureae, candidus, vaccinae, diphteriticus, septicus, bombycis, fulvus, phosphoreus.

According to our present knowledge only 5 of these 14 species (*M. luteus, aurantiacus, cyaneus, ureae,* and *candidus*) are really Micrococci. That such conspicuous characters as the motility of *B. prodigiosus* or the pleomorphous nature of *Myxococcus fulvus*—*Jahn* (1909–1911, pp. 191 and 198) has shown that this, indeed, is what *Cohn* called *Microc. fulvus*—have not been noticed by *F. Cohn* sufficiently proves our point.

The German botanists who, like *Winter* (1884) and *Schroeter* (1886), otherwise closely adhered to *Cohn*, did not accept his genera as "natural" ones. *Winter* (p. 36) says that several of *Cohn's* genera are merely developmental stages of other genera and that many of his species probably are nothing else than more or less constant modifications, split up from one species under different environmental conditions. *Schroeter*, too, was of the opinion (p. 140) that the form of the individual cells very often change in the course of their development. They all must be known before the true character of a species can be defined.

As *Robert Koch* in the early part of his bacteriological work was greatly influenced by *F. Cohn* just at the time when this author had left his earlier, more cautious standpoint, naturally the monomorphistic view was readily adopted. In his "Untersuchungen über die Aetiologie der Wundkrankheiten" (1878) the following statement is made (English translation, p. 71):

In all my experiments not only have the form and size of the bacteria been constant, but the greatest uniformity in their action on the animal organism has been observed.

Constancy of form and action became a dogma, which was upheld for the next decades more by *R. Koch's* pupils than by himself. That in many cases constancy of action is missing

was soon shown by French bacteriologists under the leadership of *Pasteur*. And the question whether or not separate species should and can be based on the frequently very small differences found has been left unanswered by *R. Koch*. On account of practical reasons he emphasized the necessity of making as many divisions as were indicated by differences of form or action. But he did not care whether these now might represent "species, or varieties, or forms, or what else one should like to call them" (1881, p. 31). And later he was even quite willing to admit the variability of the bacteria (1890):

Innerhalb gewisser Grenzen können Abweichungen von dem gewöhnlichen Typus der Art bei den Bakterien und insbesondere auch bei den pathogenen Bakterien vorkommen.

Strictest constancy of form and action was first proclaimed by *Gaffky* (1881). To him it was unquestionable that any change which might occur was caused by the overgrowing of one species by another. Though *Friedländer* (1883) found that his "Mikrokokken der Pneumonie" (now usually called *B. pneumoniae*) can grow either in distinctly globular, oval, or in rod-like form of different length, *Flügge* (1884) did not hesitate to declare:

Niemals haben wir beobachten können, dass wirkliche Cokken in Bacillen sich umwandeln und umgekehrt.

In the same publication this author makes also another characteristic statement which later has caused much unnecessary confusion:

Wenn Thatsachen gefunden wären, aus welchen die Wandelbarkeit der Infectionserreger gefolgert werden müsste, so würden wir . . . auf eine weitere experimentelle Erforschung der Infectionskrankheiten verzichten müssen.

Buchner (1885), however, correctly pointed out that the disputed constancy of form and action has nothing whatever to do with the indisputed constancy of species. Nevertheless, this logical mistake is even to-day not yet quite eliminated.

The "Bacteriologische Diagnostik," published by *J. Eisenberg* in 1890, gives a very characteristic picture of the German literature as it was written at that time by *R. Koch's* pupils. Even such highly pleomorphous organisms like the diphtheria and tubercle bacilli were considered to be correctly described as follows:

Diphtheria bacillus (p.237): "Teils gerade, teils leicht gebogene Stäbchen von der Länge der Tuberkelbacillen, jedoch etwa doppelt so dick. In gefärbten Präparaten durch überwiegende Farbstoffaufnahme an den Enden hantelförmig."

Tubercle bacillus (p. 253): "Sehr dünne, 2–5μ lange Stäbchen, meist leicht gekrümmt."

The following two statements of *C. Fränkel* (1891, pp. 12 and 169) are equally interesting. The constancy of action is not longer upheld, but *Flügge's* logical mistake is renewed:

Bisher ist eine vielförmige Bakterienart nicht zur Beobachtung gelangt, und der Satz "Man kann unter den Bakterien nach Wirkung und Form scharf unterschiedene Gattungen und Arten erkennen, welche nicht in einander übergehen" bleibt zu Recht bestehen.—Freilich ist die Grenze, die wir zwischen pathogenen und nicht pathogenen Bakterien ziehen, keineswegs eine feste und unverrückbare. Eine ganze Anzahl von Mikroorganismen, die gewöhnlich ganz harmlosen Character zeigen, vermögen unter Umständen auch eine pathogene Rolle zu spielen, und ebenso kann manche pathogene Art ihre gewöhnlichen Eigenschaften ablegen und in die Reihe der unschädlichen Bakterien übertreten.

Gotschlich (1903–1909) and *Günther* (1906) once more tried to support the "morphologische Grundgesetz" of the constancy of the form as proclaimed by *Cohn* and *Koch*, though a considerable number of contradictory results now had to be admitted. *Günther* accepts already for the different species not a constant form, but a constant form cycle. But he still thinks the constancy of the form is indisputable, because there is no "unlimited" morphological variability (1906, p. 22).

Among the German botanists the monomorphistic theory also gained some temporary foothold.

When *Brefeld* in 1881 first entered the subject, he wrote quite correctly, similar to *Nägeli* (p 50):

Die Untersuchung von Spaltpizformen muss . . . entwicklungsgeschichtlich . . . in Angriff genommen werden, wenn eine natürliche Systematik . . . begründet werden soll. Die vorläufigen Einzelheiten reichen dafür auch nicht von ferne aus.

Later, however, his standpoint was quite different (1908, pp. 99–100):

In rein morphologischer Beziehung bieten die Bakterien nach ihrer einfachen Formbildung und der stereotypen Art ihrer Teilung und Vermehrung wenig Bemerkenswertes dar . . . Die Ziele der Kultur bei den Fadenpilzen,

die Höhe der vegetativen Bildung zu erreichen und dann die verschiedenen Fruchtformen auf dem Wege der Kultur aus den vegetativen Zuständen zu gewinnen, ihre Zusammengehörigkeit zu den einzelnen Formen der höheren Pilze sicher festzustellen, liegt bei den Bakterien von vornherein ausserhalb der Fragestellung.

A. Fischer (1903, p. 44), as well as *A. Meyer* (1912, p. 61), take also their stand against the pleomorphism, though, of course, they do not dispute the variability of the cell form. *Benecke* (1912, p. 216) says:

Jede Art hat ihren Variabilitätskreis, der grösser oder kleiner sein kann.

The very numerous papers on variation, mutation, etc., contained in the German literature of the last decade, will have to be discussed later. Taken together, they furnish convincing proof that the monomorphistic theory of *Cohn* and *Koch* has become utterly untenable.

However, more or less opposition has always been put forward by other German and Austrian bacteriologists, though the very important practical results attained by *R. Koch* and his pupils have materially helped to keep their antagonists temporarily in the background.

Neelsen (1880) drew the following conclusion from his studies upon *B. cyanogenes*, which are of special interest because this work was done in *F. Cohn's* laboratory and published as the tenth contribution to his "Untersuchungen über Bacterien." It is stated therein (p. 242):

dass die von *Cohn* aufgestellten Gattungen insofern zu eng begrenzt sind, als ein Organismus in seinem Lebenscyclus verschiedene der als getrennt hingestellten Formen vereinigen kann.

Haberkorn (1882) emphasized correctly that the hypothesis of simplicity and constancy of form was not well founded. Unfortunately his own experiments, though very interesting, are open to the same criticism. But he was right when he wrote:

Richtiger, d. h. der Wissenschaft förderlicher ist, beim Forschen noch Lücken im Entwicklungsgange vorauszusetzen, als voreilig den genetischen Cyclus abzuschliessen.

Miller's (1882) investigations upon the bacteria of the human mouth, *Kurth's* (1883) isolation of *Bacterium Zopfii,* growing in globular, rod-like and spiral form, *Hauser's* (1885) discovery of his three Proteus forms, first considered to be different species, later (*Hauser,* 1892) acknowledged as modifications of one species, *Biedert's* (1885) and *Malapert-Neufville's* (1886) studies upon other pleomorphic bacteria from mouth and water, furnished additional proof that pleomorphism does by no means obscure, but even enhances the well defined character of a species. *DeBary* (1884) also declared, that doubtless different species have to be distinguished with the bacteria as with the higher organisms. Some of them may exhibit a relatively monomorphous character, while others may be distinctly pleomorphic.

The most prominent place among the German adversaries of *Cohn's* and *Koch's* standpoint has been taken by *Zopf* (1881–1885). It is true that many of his ideas have been gathered from studies done with species (especially with thread-bacteria) which have not very much in common with the pathogenic microbes *Koch* was interested in. Nevertheless, his opposition against the extreme monomorphism was sufficiently supported by well ascertained facts, and he was equally right when he emphasized, like *Nägeli* and *Buchner,* that as long as the complete life history of the bacteria remained unknown no correct systematic arrangement could be made.

More well-founded criticism concerning the alleged constancy of form was furnished by *Gruber* (1885, 1894), *Firtsch* (1888), and *Escherich* (1886). The last-named author says, that now, after *Koch's* methods have made it possible to study rigorously pure cultures, more and more bacteriologists are inclined to accept the pleomorphistic point of view.

Rosenbach's publications on the causative agent of the so-called erysipeloid exemplify in a very interesting manner how extended research may completely change the situation. In 1884 he described the organism as a *Micrococcus;* in 1887 he declared it to be a peculiar branching organism probably related to *Cladothrix* (Streptothrix), and in 1909 he showed that it represented a variety of *Bact. erysipelatos suum,* of which he discovered the full very polymorphous life cycle.

The following quotations from *Hueppe's* writings are equally interesting. In 1883 he criticized *Zopf's* standpoint in a very sharp manner, very much like *Flügge* (1884). No change from a coccus to a bacillus or vice versa could be accepted, and the idea that the tubercle bacillus might be related to any "thrix" was declared to be entirely absurd. Ten years later *F. Fischel*

(1893) secured conclusive proof for this relationship by his investigations carried out under *Hueppe's* direction. But already in 1886 *Hueppe's* own standpoint had undergone considerable modification. The "dogmatic onesidedness" (p. 85), which knows nothing but strict constancy of form or unlimited variability, was now refuted and it was said (p.61):

Wenn auch die einzelnen Formen sich bald mehr bald weniger mit den Aussenbedingungen ändern können . . so tritt doch unter denselben Verhältnissen immer ein ziemlich scharf bestimmter, bald enger, bald weiter Formenkreis auf.

In 1891 (pp. 22, 27) the occurrence of all different cell forms within the life cycle of the same organism was still more readily admitted by *Hueppe.* And in 1896 *Zopf's* standpoint has been practically reached (p. 15):

Die starren Formarten, wie sie . . . *Cohn, Schroeter,* und *Koch* angenommen hatten, haben sich nicht aufrecht erhalten lassen. Die Anpassungsfähigkeit der Bakterienformen bei Wechsel der Ernährungsbedingungen ist . . . beträchtlich grösser, als man früher mit dem Begriffe konstanter Arten für vereinbar gehalten hatte.

Migula was at first also very much opposed against all "pleomorphistischen Gelüste' (1897, Vol. I, p. 18). He taught (l. c., p. 50):

Die Bakterien zeigen eine grosse Einförmigkeit. Drei Gestalten sind es, welche uns immer wieder bei ihnen entgegentreten: die Kugel, das cylindrische und das schraubig gekrümmte Stäbchen.

But in the same book (p. 236) he also wrote:

Inwieweit die einzelnen Arten verschiedene Formen zu bilden vermögen, muss der weiteren Forschung vorbehalten bleiben; unsere gegenwärtige Kenntnis davon ist im höchsten Grade lückenhaft.

In 1904 he admitted in *Lafar's* "Handbuch" (Vol. I, p. 42) that the monomorphistic theory had to be abandoned. The same statement had been made by *Lafar* himself in 1897 (p. 36), and since then it has been amply confirmed by the results of practically all investigations made along these lines by German and Austrian bacteriologists. The present situation is correctly described in the following quotation from *Lehmann* and *Neumann* (1912, pp. 146–149):

Die Cohnsche Lehre von der Konstanz der Arten . . . wird heute in immer weiterem Umfange unhaltbar. Denn die fortgesetzte, immer tiefer gehende Forschung hat zur Evidenz erwiesen, dass fast alle Eigenschaften einer wohlumgrenzten Art sehr schwanken. . . . Wir glauben sicher, dass es der Zukunft noch in heute kaum geahnter Weise gelingen wird, Bakterienarten in einander überzuführen. . . . Die Lehre von der absoluten Unveränderlichkeit der Bakterien, die vor 20 Jahren noch fast als Dogma galt, wird heute kaum mehr ernsthaft vertreten.

The old extreme pleomorphism of *Hallier* has been also revived in the German literature from time to time. *Hallier* himself reiterated his former statements in 1895 and 1896, which he now thought to be "in complete agreement with *R. Koch's* discoveries." *J. Müller* published a similar work in 1898. To him the bacteria are still the offspring of the spermata of different fungi, though already in 1869 *H. Hoffmann* had proven that this is not the case. Equally erroneous were the discoveries of *Stutzer* and *Hartleb* (1897) concerning their highly pleomorphic "Salpeterpilz" (a complex mixture of various fungi and bacteria, as was shown in 1898 by *Gaertner, Fraenkel,* and *Krueger*) and their "Bakterium der Maul- und Klauenseuche." *Niessen's* "Syphilomyces" (1908) belongs in the same class. *Dunbar's* book "Zur Frage der Stellung der Bakterien, Hefen und Schimmelpilze im System" (1907), which apparently confirmed many of the old statements of *Trécul, Béchamp, Bastian, Hallier,* and others, elicited the following characteristic remark from *Pringsheim* (1910, p. 139):

Bei solchen Behauptungen fasst man sich an den Kopf, um sich zu versichern, dass er noch auf den Schultern sitzt. Das ganze Gebäude unserer Wissenschaft droht zusammenzustürzen.

As I will have to show in Chapter II, the knowledge of the formation and development of the bacterial gonidia helps to make these so far unexplainable observations quite intelligible.

The standpoint taken by the bacteriologists in other European countries is mostly on the pleomorphistic side.

In Switzerland *Perty* (1852) has furnished one of the earliest contributions to the knowledge of the life history of the bacteria, especially concerning their upgrowth from the gonidial stage. More recently *Düggeli* (1905) discussed the question of the systematic arrangement of the bacteria, closely agreeing with *Lehmann* and *Neumann.*

In Italy the view, once held by *Robin,* that the different cocci and rods merely represent stages in the development of *Leptothrix buccalis* was renewed by *Vincentini* (1893), to whom pneumococci and tubercle bacilli were only types of growth of a *Leptothrix racemosa.* In Naples

Schroen made several important investigations, to which we will have to refer later. This also will be the case with the work done by *Ferrán* in Spain.

Gedoelst (1899) in Belgium shared the standpoint taken by his French colleagues. *Fokker* in Holland took his place at the side of *Trécul* and *Béchamp*. He was one of the earliest opponents (1882) of the constancy dogma of *Cohn* and *Koch*. Recently *E. de Negri* in Utrecht discovered the complete life cycle of the Corynebacteria (1916).

In Denmark the work done by *Lankester* in England was confirmed by *Warming*, who concluded (1876, p. 10):

Les bactéries sont données en réalité d'une plasticité illimitée, et je crois qu'il faudra renoncer au système de M. Cohn et de quelques autres savants, qui caracterisent les genres et les espèces d'après leur forme.

E. Chr. Hansen in Copenhagen discovered the pleomorphism of the acetic acid bacteria. *Schmidt* and *Weis* (1902, p. 78) also discussed the inconstancy of the cell form. *Jörgensen* (1911) wrote in his textbook (English translation, p. 78):

A single species of bacteria may occur in various forms, and this may happen either during the normal growth of the vegetation, or in growths on different media.

In Norway the strictly monomorphistic side was represented by *G. A. Hansen*. As late as in 1903 he still rejected as unreliable all reports on irregular, especially on branched forms of tubercle and leprosy organisms. On the other hand, *Olsen* (1897) has furnished very interesting data supporting the pleomorphistic point of view. In his opinion, probably all bacteria, at least all bacilli, are able to exhibit under favorable conditions a branched, mycelial growth.

Still more important contributions have been made by *Almquist* and his pupils in Sweden. He is one of the few authors, who discovered independently the complete life cycles of different pathogenic bacteria. Much valuable material is contained in a long series of his publications (1893–1917).

In Russia as early as 1877 *Cienkowski* has proved convincingly that *Cohn's* form genera were untenable. *Winogradsky*, on the other side, strongly defended in his early papers (1887–1889) the strictest monomorphism against *Lankester*, *Warming*, *Zopf*, *Metchnikoff*, and others, though he admits that further experimenting perhaps might change the situation. In fact, his own nvestigations upon the nitrite bacteria (1892) did not support his monomorphistic standpoint. Within the same species the cell forms varied to such an extent that, as he says—

On croiraît sûrement avoir affaire à des organismes différents. Il n'en est pourtant rien.

In America at first the French standpoint won some influence by *G. M. Sternberg's* edition of *Magnin's* textbook (1884). Later, however, following *Baumgarten* (1890) the bacteria were divided by *Sternberg* (1896) into two groups: I. Relatively monomorphous; II. Pleomorphous organisms. *H. L. Russell* (1892) found among marine bacteria considerable morphological variation. *Th. Smith* (1890–1900) studied the various factors modifying the development of different pathogenic organisms and took his stand against the reckless "species" making. *Hopkins* (1898) isolated apparently the same pleomorphous mouth bacterium which had been studied in Germany by *Biedert* (1885). Although it clearly grows either in globular or in rod-like form according to the environment, the author emphasizes that "it is not positively asserted that a rod can be produced from a coccus, nor a coccus from a rod." *H. W. Conn* (1900) made some interesting observations upon the wide physiological variability in pure cultures of micrococci. *N. G. Davis* (1901) got a typical coccus from *Bac. rosaceus metalloides*. *Ohlmacher* (1902) isolated from a colon septicaemia a colon bacillus exhibiting a "truly astonishing" pleomorphism. The task of making a detailed description of all the various shapes assumed by this bacillus, he declares "well-nigh impossible."

In spite of these and other contributions of American bacteriologists, there are, however, only comparatively few American textbooks which do not adhere to the rigid monomorphism which had been taught in Germany.

The inconstancy of form and action has been advocated by *Chester* (1901), to whom (p. 51) "one form appears to merge into another," and by *E. F. Smith* (1905), who says (p. 177):

We know that bacteria are much more responsive to changed environment than was supposed by *Koch* and his followers in the eighties, and we are prepared to believe anything respecting their origin and their polymorphism which can gain the suffrage of the great body of critical workers who now cultivate this field.

On the other hand, *A. C. Abbott,* (1902, p. 51) emphasizes:

One can never produce bacilli from micrococci, nor vice versa; and any evidence which may be presented to the contrary, is based upon untrustworthy methods of observation.

Like to *Cohn, Koch,* and their followers, to *Ball* (1908), as well as to *Frost* and *McCampbell* (1910), a change in cell morphology is synonymous to a change of species or genus. Accordingly, statements like these are made:

A bacillus does not arise from a micrococcus or the typhoid fever bacillus produce the bacillus of tetanus.—(*Ball,* p. 23.)

It is not possible to cause any permant change in the morphology of a bacterium and thus originate a new species of bacteria. For example, it is not possible to cause a bacillus to change into a coccus and vice versa.—(*Frost* and *McCampbell,* p. 25.)

Though not quite in such dogmatic terms, constancy of form is also advocated by *Jordan* (1909, p. 54; 1916, p. 65):

Under normal and uniform conditions of life each form breeds true, the spherical forms producing only spheres and the rods, again, only rods.

Concerning the plague bacillus, however, it is said (1916, p. 321):

Many morphologic variations, coccus shapes and large rods, are found.

The standpoint taken by *Park* and *Williams* (1914 p. 31) is similar:

Micrococci always, under suitable conditions, produce micrococci, bacilli produce bacilli, and spirilla produce spirilla.

Nevertheless, the variability of the cell form is more adequately discussed in this work. Of special interest is a picture (p. 294, fig. 119) showing a variety of diphtheria bacilli which grows exclusively in the form of a large coccus.

Hiss and *Zinsser* (1914, p. 19) say:

Variations from the basic forms may occur, but are not common among bacteria under normal conditions.

Kendall (1916, p. 21) repeats the statement made by *Jordan* and adds (p. 23):

Given constant conditions, bacteria growing in a favorable environment exhibit constancy of form and size, although a few organisms in every culture are somewhat larger or smaller than their fellows, appearing as occasional giants or dwarfs.

Pleomorphism is said (p. 24) to be "rarely or never met with among the pathogenic bacteria." However, the diptheria bacillus is declared (p. 389) to be "highly pleiomorphic" and the plague bacillus (p. 408) "very pleiomorphic."

In recent American literature generally the interest has been centered more upon physiological than morphological problems. *Orla Jensen's* so-called natural system of the bacteria, almost entirely based on mere biochemical hypothesis, has been accepted, for instance, by *Jordan* (1916 p. 197) as "a promising beginning in classifying bacteria." Accordingly, morphological questions are not infrequently left without adequate consideration. When describing the characters of the different Colon varieties *Rogers* says, in the first of two papers published in 1914, that in the morphology of *B. coli* there is "so little variation that no attempt was made to use this character in differentiation;" whereas he states in the second: "There is a wide variation in both the size and the form of the cell, but since these variations frequently occur within the limits of a single culture they are without varietal significance." The microscopic tests have been made only once with the cultures when 24 hours old, and the motility was not determined at all, as it was considered to be too unstable.

Several important contributions to our subject, however, have been made more recently by American authors. *Noguchi* (1910) proved for the first time that it is possible to transform a nonspore-forming lactobaccillus into a spore-forming member of the Mesentericus group, which fact, though quite probable (*Löhnis,* 1910, p. 200), has never before been tested experimentally. *Maher* (1910–1915) furnished some interesting details concerning the complete life cycle of the tubercle bacillus. Unfortunately, there are some entirely unfounded hypotheses interspersed in his work, which obviously have caused the valuable observations contained therein to be passed practically unnoticed.

The very important contributions, which have been made by *Rosenow* and his coworkers (1912–1917), deserve special discussion on the following pages, like those of *Almquist* and of *Hort*.

(*b*) CAUSES OF APPARENT AND OF GENUINE PLEOMORPHISM.

Before proceeding to review the various explanations given by different authors concerning the much disputed pleomorphism of the bacteria, it seems advisable, to arrange for ready reference in Table I a list of papers wherein data about the pleomorphism shown by the different groups of bacteria may be found. As the presence of branching forms has been frequently considered to be of special importance in regard to the morphology and the systematic position of the bacteria concerned, observations made in this direction have been mentioned in a special column.

TABLE I.

Organisms.	Different cell forms observed.	Branching observed.
Meningococcus	Lehmann and Neumann, 1912; Hort et al, 1915–1916	
Gonococcus	Herzog, 1913	
M. melitensis	Durham, 1898; Babes, 1903; Günther, 1906; Saisawa, 1911; Lehmann and Neumann, 1912; Jordan, 1916, Evans, 1918.	
M. candicans	Löhnis and Smith, 1916	Löhnis-Smith, 1916.
M. flavus	Matzuschita, 1900	Matzuschita, 1900.
M. subnormalis	Hopkins, 1898	
M. rubefaciens	Matzuschita, 1900	Matzuschita, 1900.
M. cyaneus	Beijerinck, 1914	
M. viticulosus	Lehmann and Neumann, 1912	
Sarcinae spec	Lehmann and Neumann, 1912; Löhnis and Smith, 1916	
Urosarcina	Beijerinck, 1901; Miquel and Cambier, 1902	
Sarcinastrum	Lagerheim, 1900	
Pneumococcus and Streptoc. pyogenes	Pansini, 1890; Kruse and Pansini, 1892; Arloing and Chantre, 1894; Babes, 1895; Crookshank, 1896; Stolz, 1898; Ohlmacher, 1902; Taddei, 1909; Broadhurst, 1915, Mallory and Medlar, 1916.	Babes, 1896; Seitz, 1896; Crookshank, 1896; Stolz, 1898; Vincent, 1902, Kraskowska and Nitsch, 1918.
Streptoc. lactis	Billroth, 1874; Maddox, 1885; Burri, 1898; Düggeli, 1905; Löhnis, 1907; Wolff, 1908.	
Poliomyelitis	Rosenow et al., 1916–1917; Nuzum, 1916; Mathers, 1917	
Enterococcus	Thiercelin, 1899–1903	
Leuconostoc	Van Tieghem, 1879 *c*; Ludwig, 1896; Hlava, 1902	
Proteus	Hauser, 1885; Jaeger, 1892; Kohlbrugge, 1901; Höflich, 1902; Matzuschita, 1902; Stefansky, 1902.	Matzuschita, 1902; Stefansky, 1902.
Bact. Zopfii	Kurth, 1883; Schedtler, 1887	Schedtler, 1887.
B. acidophilus bifidus etc.	Sternberg, 1898; Moro, 1900; Tissier, 1900; Cahn, 1901; Rodella, 1901–1908; Sandberg 1904; Noguchi, 1910; Blühdorn, 1910; Bertrand, 1913.	Moro, 1900; Tissier, 1900; Cahn 1901; Blühdorn, 1910.
Lactobacilli from milk, cheese, etc.	Henneberg, 1901; Holliger, 1902; Freudenreich and Thöni, 1905; Düggeli, 1905; Löhnis, 1907; Heinemann and Hefferan, 1909; Rubinsky, 1910; Chatterji, 1910; Koegel, 1914.	Freudenreich and Thöni, 1905; Heinemann and Hefferan, 1909; Rubinsky, 1910.
B. acidi propionici b.	Freudenreich and Jensen, 1906	
B. funduliformis group	Hallé, 1898; Ghon and Sachs, 1905; Ghon, Mucha and Müller, 1906; Kisskalt, 1906.	Hallé, 1898; Ghon and Sachs, 1905.
B. erysipelatos	Karlinski, 1889; Rosenbach, 1909	Rosenbach, 1909.
B. septicaemiae (Pasteurella)	Rosenfeld, 1901; Nowak, 1908	Rosenfeld, Phisalix, 1902, Nowak.
B. pseudotuberc. rodentium	Galli-Valerio, 1903, 1913; Zlatogoroff, 1904	Galli-Valerio, 1903.
Bact. pestis	Albrecht and Ghon, 1900; Skschivan, 1900; Cacace, 1903; Dieudonné, 1903; Galli-Valerio, 1903; Zlatogoroff, 1904; Rowland, 1912–1914.	Albrecht and Ghon, Skschivan, Cacace, Dieudonné, Galli-Valerio, Kodama, 1908; Rowland, 1914.
B. influenzae	Crookshank, 1896; Grassberger, 1898; Davis, 1907	Grassberger 1898.
B. pneunomiae, ozaenae, etc.	Bordoni-Uffreduzzi, 1888; Simoni, 1900; Jehle, 1902; Lepeschkin, 1904; Löhnis, 1905; Péju and Rajat, 1906; Toenniessen, 1913; Ward, 1917.	Bordoni-Uffreduzzi, 1888; Lepeschkin, 1904; Löhnis, 1905.
B. coli	Haslam, 1898; Adami et al., 1899; M. E. Abbott, 1900; Matzuschita, 1900; Ohlmacher, 1902; Péju and Rajat, 1906; Wilson, 1907; Revis, 1912; Kellerman and Scales, 1916; Prell, 1917.	Walker and Murray, 1904; Wilson, 1907.
B. dysenteriae	Péju and Rajat, 1906; Hata, 1908; Almquist, 1917	Hata, 1908.
B. typhi	Almquist, 1893; 1894, 1916; Walker and Murray, 1904; Péju and Rajat, 1906; Wilson, 1907.	Gamaleia, 1900; Casagrandi, 1901; Almquist; Walker and Murray, 1904; Wilson, 1907.
B. radiobacter and radicicola	Beijerinck, 1888, 1890; Prazmoski, 1890; Hiltner and Störmer, 1903; Löhnis, 1905; Rossi, 1907; Harrison and Barlow, 1907; Georgewitch, 1916.	Beijerinck; Dawson, 1899; Hiltner and Störmer; Löhnis; Harrison and Barlow, Conn, 1909.
B. rubiacearum	Faber, 1912; Georgevitch, 1916	Faber, Georgevitch.
B. tumefaciens	E. F. Smith, 1911	E. F. Smith, 1911.
Acetic acid bacteria	Hansen, 1879, 1894; Zeidler, 1896; Henneberg, 1897, 1898; Janke, 1916.	Henneberg, 1897, 1898.
Photobacteria	Beijerinck, 1889; Barnard, 1899; Molisch, 1903, 1904; Reinelt, 1905.	Beijerinck, 1889; Barnard, 1899.
Bact. solare	E. Wolff, 1898	E. Wolff, 1898.
B. Fraenkelii	Hashimoto, 1899	Hashimoto, 1899.
B. prodigiosum	Wasserzug, 1888; Slater, 1891; Davis, 1901	Slater, 1891.
B. violaceum	Zopf, 1885; Harrison and Barlow, 1905	Harrison and Barlow, 1905.
B. fluorescens and pyocyaneum	Guignard and Charrin, 1887; Schürmayer, 1895; Wassermann, 1903; Wilson, 1907; Löhnis and Smith, 1916.	Gamaleia, 1900; Wilson, 1907; Löhnis and Smith, 1916.
Ps. cerevisiae	Fuhrmann, 1906	
B. ferrugineum	Rullmann, 1897–1900	Rullmann, 1897–1900.
Nitrosomonas	Winogradsky, 1892	
Nitrobacter	Winogradsky, 1891	
B. mycoides	Olsen, 1897; Nadson and Adamovic, 1912	Olsen. 1897.
B. anthracis	E. Klein, 1883, 1885; DeBary, 1884; Braem, 1889; Rodet, 1894; Crookshank, 1896; Matzuschita, 1900; Lignières and Durrieu, 1902; Henri, 1914.	Lignieres and Durrieu, 1902; Henri. 1914.
B, subtilis	Klein 1885; Löhnis and Smith, 1916	Löhnis and Smith, 1916.
Tyrothrix	Duclaux, 1883; Winkler, 1895	
B. cohaerens	Gottheil, 1901	Gottheil, 1901; A. Meyer. 1901.

Table I—Continued.

Organisms.	Different cell forms observed.	Branching observed.
B. mesentericus	Löhnis and Smith, 1916	Löhnis and Smith, 1916.
B. megaterium	DeBary, 1884; Stoklasa, 1898; Lehmann and Neumann, 1912	Gamaleia, 1900.
B. tumescens	Zopf, 1883; A. Koch, 1888; Garbowski, 1907	
B. oxalaticus	Kuntze, 1904	
B. malabarensis	Löhnis and Pillai, 1907	
B. azotobacter	Beijerinck, 1901; H. Fischer, 1905; Löhnis and Westermann, 1908; Krzemieniewski, 1908; Peklo, 1910; Prazmowski, 1912; Löhnis and Hanzawa, 1914; Löhnis and Smith, 1916.	H. Fischer, 1905; Löhnis and Westermann, 1908; Löhnis and Smith, 1916.
Other aerobic spore-forming bacilli.	Pansini, 1890; Russell, 1892; Niessen, 1898; Gottheil, 1901; Miquel and Cambier, 1902; Neide, 1904; Maassen, 1904; Garbowski, 1907; Proca and Danila, 1910; Viehoever, 1913; Löhnis and Smith, 1916.	Niessen, 1898; Maassen, 1904; Löhnis and Smith, 1916.
B. alvei	Harrison, 1900	Harrison, 1900.
B. amylobacter	Prazmowski, 1880; Buchner, 1882; Van Tieghem, 1884; Schattenfroh and Grassberger, 1900; Winogradsky, 1902; Grassberger, 1902, 1905; Grassberger and Schattenfroh, 1907.	
B. Chauvoei	Ehlers, 1884; Fraenkel and Pfeiffer, 1895; Piani and Galli-Valerio, 1895; Ghon and Sachs, 1903; Grassberger, 1903, 1905; Grassberger and Schattenfroh, 1907; Hibler, 1908.	Ghon and Sachs, 1903.
B. oedematis	Grassberger, 1903; Ghon and Mucha, 1905	Grassberger; Ghon and Mucha.
Cellulose bacilli	Prazmowski, 1880; Omelianski, 1902	
B. tetani	Kanthack and Connell, 1897; Hibler, 1908	Kanthack, 1896; Tavel, 1898.
Vibrio cholerae	E. Klein, 1885 a; Ferrán, 1885; Ermengem, 1885; Dowdeswell, 1889, 1890; Friedrich, 1892; Metchnikoff, 1894; Gruber, 1894; Fraenkel and Pfeiffer, 1895; Cunningham, 1897; Nakanishi, 1900; Gamaleia, 1903; Kolle and Gotschlich, 1903; Almquist, 1904, 1907; Hammerl, 1906; Baerthlein, 1912; Lehmann and Neumann, 1912; Stamm, 1914; Popoff-Tscherkasky, 1914; Olsson, 1915.	Dowdeswell, 1889; Metchnikoff, 1894; Kohlbrugge, 1901; Shibayama, 1902, Hammerl, 1906; Stamm, 1914.
V. cardii	E. Klein, 1905	
V. proteus Buchner	Finkler and Prior, 1884, 1885; Firtsch, 1888; Fuerst, 1914	
V. proteus Kohlbrugge	Kohlbrugge, 1900	Kohlbrugge, 1901.
V. Metchnikovii	Nakanishi, 1901	
V. Rugula	Bonhoff, 1896	Bonhoff, 1896.
V. phosphorescens	Maassen, 1904	Maassen, 1904.
V. saprophiles	Weibel, 1888	
V. nasalis	Weibel, 1888	
V. lingualis	Weibel, 1888	Bajardi, 1903.
Spirillum undula	Kutscher, 1895; Lehmann and Neumann, 1912	Kutscher, 1895.
Spir. rubrum	Meirowsky, 1914	Reichenbach, 1901; Meirowsky, 1914.
Sp. endoparagogicum		Sorokin, 1887, 1890.
Spir. bataviae		Faber, 1912.
Spir. pyogenes	Doerr, 1905	Doerr, 1905.
Sp. tyrogenum	Meirowsky, 1914	Meirowsky, 1914.
Spirochaeta pallida	Wechselmann and Loewenthal, 1905; Sobernheim, 1907; Krzysztalowicz and Siedlecki, 1908; Meirowsky, 1914.	Meirowsky, 1914.
Sp. gallinarum	Hindle, 1911	Meirowsky, 1914.
Sp. balanitidis		Meirowsky, 1914.
Sp. Obermeieri	Sobernheim, 1907; Karwacki, 1912	
Sp. icterohaemorrhagica	Inada et al., 1916	Inada et al., 1916.
Spiroch. suis	Ruether, 1910	
Abortus bacillus	Preisz, 1903	Preisz, 1903.
Necrosis bacillus	Schmorl, 1891; W. Ernst, 1902	Schmorl, 1891; W. Ernst, 1902.
Streptob. pellagrae	Tizzoni and Angelis, 1913–1915	Tizzoni and Angelis.
Glanders bacillus	Th. Smith, 1890; Semmer, 1895; Marx, 1899; Galli-Valerio, 1899, 1900; Conradi, 1900.	Semmer, Marx, Galli-Valerio, Conradi.
B. diptheriae	Zarniko, 1889; Escherich, 1894; Zupnik, 1897; Madsen, 1897; Meyerhof, 1898; Kurth, 1898; Wesbrook et al., 1900; Ohlmacher, 1902; Beck, 1903; Spirig, 1903; Goodman, 1908; Smirnow, 1908; Dale, 1910; Balfour, 1911d; Morse, 1912; Baerthlein, 1913; Bernhardt and Paneth, 1913; Park and Williams, 1914; Heinemann, 1917; Bergstrand, 1918.	E. Klein, 1890, 1894; Fraenkel, 1895; Bernheim and Folger, 1896; Kanthack, 1896; Meyerhof, 1898; Kurth, 1898; Hill, 1899, 1902; Cache, 1901; Concetti, 1901; Beck, 1903; Cappellani, 1910; Park, 1914; Bergstrand, 1918.
Diphtheroid bacilli	Escherich, 1894; Seitz, 1896; E. Klein, 1900; Nakanishi, 1900; Morse, 1912; Bernhardt and Paneth, 1913; Trautmann and Gaethgens, 1913; Negri and Mieremet, 1913; Lanford, 1914; E. Negri, 1916; Walker and Adkinson, 1917; Mellon, 1917.	Babes, 1895; Kanthack, 1896; Nakanishi, 1900.
B. leprae	Babes, 1883; Lutz, 1886; Bordoni-Uffreduzzi, 1888; E. Levy, 1897; Czaplewski, 1898; Teich, 1899; Barannikow, 1900, 1902; Kedrowski, 1901, 10; Babes, 1907; T. S. Williams, 1911; Galli-Valerio, 1912; Reenstjerna, 1912; Wolbach and Honeij, 1914.	Czaplewski, 1898; Kedrowski, 1901, 1910; T. S. Williams, 1911; Johnston, 1917.
B. tuberculosis	Klebs, 1883; Babes, 1883; Zopf, 1883; Malassez and Vignal, 1884; Lutz, 1886; Metchnikoff, 1888; Cornil and Babes, 1890; F. Fischel, 1893; Coppen-Jones, 1893, 1895; Bruns, 1895; Semmer, 1895; Olsen, 1897; Babes and Levaditi, 1897; Marpmann, 1897; Ferrán, 1897; Schumowski, 1898, 1899; Schuermayer, 1898; Schulze, 1899; Lubarsch, 1899; Arrigo, 1900; Courmont and Descos, 1902; Herzog, 1903; Wolbach and Ernst, 1903; Hawthorn, 1903; Schroen, 1904; Picry and Mandoul, 1904; Arloing, 1908; Betegh, 1908; Much, 1908, 1909; Maher, 1910–1915; Kryloff, 1911; Galli-Valerio, 1912; Wherry, 1913.	Metchnikoff, 1888; E. Klein, 1890, 1894; Mafucci, 1892; F. Fischel, 1893; Coppen-Jones, 1893, 1895; Semmer, 1895; Kanthack, 1896; Olsen, 1897; Marpmann, 1897; Schuermayer, 1898; Dorset, 1901; Wolbach and Ernst, 1903; Schroen, 1904; Miehe, 1908; Galli-Valerio, 1912.
Pseudo-tuberculosis bacilli	Preisz, 1894; Korn, 1899; Moëller, 1899; Lubarsch, 1899; Bongert, 1901; Abbott and Gildersleeve, 1902; Courmont and Descos, 1902; Schabad, 1904; Sanfelice, 1905.	Korn, 1899; Schabad, 1904; Sanfelice, 1905.
Mycobacterium spec	Söhngen, 1913; Chantemesse et al., 1917	Söhngen, 1913; Chantemesse et al., 1917.
Actinomyces spec	Bollinger, 1877; J. Israël, 1878; O. Israël, 1884; Nocard, 1888; McFadyean, 1889; Bostroem, 1890; Eppinger, 1890; Kedzior, 1896; Rullmann, 1896, 1898; Lachner-Sandoval, 1898; Schuermayer, 1900; Silberschmidt, 1901; Neukirch, 1902; Feistmantel, 1902; MacCallum, 1902; Doepke, 1902; Nakayama, 1906; Hollandt, 1906; Loele, 1908; Claypole, 1913; Th. Cohn, 1913; Krainsky, 1914.	All authors mentioned.
Leptothrix	Miller, 1883; Zopf, 1883, 1885; Dobrzyniecki, 1897; Beust, 1907.	Dobrzyniecki, 1897.
Cladothrix	Cohn, 1875; Zopf, 1881, 1882; Billet, 1890; Büsgen, 1894; Migula, 1900; Ellis, 1912.	Cohn, 1875; Zopf, 1882; Migula, 1900.
Beggiatoa	Zopf, 1881–1883, 1895; Engler, 1882; Billet, 1890	
Crenothrix	Zopf, 1879; Schorler, 1904	
Clonothrix	Schorler, 1904	Schorler, 1904.

There is no doubt, and the facts to be discussed later will amply support the statement, that a wide pleomorphism has been observed within all groups of the bacteria by numerous authors. And if at the present time several authors still firmly defend the morphological constancy and simplicity of the bacteria, and do not hesitate to declare beforehand that "any evidence which may be presented to the contrary is based upon untrustworthy methods of observation," we are reminded of many cases in the history of science where newly discovered facts have been strongly opposed by scientific dogmatism. When, e. g., *Sir Thomas Brown* first attacked the time-honored dogma of the spontaneous generation of mice and other vermin from putrefying material *Alexander Ross* commented on this point: "To question this is to question reason, sense, and experience" (*Frost* and *McCampbell*, p. 9). *Oznam* wrote still in 1820 against the theory of the "contagium animatum," though it was supported by men like *Kircher, Vallisneri, Réaumur, Plenciz,* and *Frémont:* "Ich will keine Zeit verlieren, diese abgeschmackten Hypothesen zu widerlegen" (*Loeffler,* 1887, p. 11). *Pineau's* (1845 *a*) remark that frequently the facts recorded "sont entachés d'un esprit de système qui perce dans les resultats" fits also remarkably well to many a report on microscopic studies done from a monomorphistic point of view.

But a great deal of the opposition which has been raised against the pleomorphistic theory was much more based on misunderstanding than on adverse facts. The old mistake to consider the acknowledgment of the occurrence of different cell forms within one species as equivalent to an acceptance of the theory of spontaneous generation or to an inclination to cancel all differentiation of species, still takes a prominent place in some textbooks despite its absurdity. In many other cases a different use of the word pleomorphism has been responsible for much useless debate. *Migula* (1897, p. 229; 1904, p. 47) and *Schmidt* and *Weis* (1902, p. 86) want to have the term restricted, as had been done by *DeBary* (1884, p. 136) for the fungi, to such cases where the complete life history of a bacterium is composed of several subcycles characterized by different morphology. Occurrence of any of the so-called involution forms should not be taken as indicative of a pleomorphous character, according to these authors. To *Migula* (1904, p. 37), however, involution forms are *all* cell forms differing from the normal appearance of the species or variety concerned, irrespective of their origin ("ohne Rücksicht auf das Zustandekommen dieser Abweichung"). Such reasoning naturally would never allow the discovery of any pleomorphism, how evident it may be. Also, in this case it is "le système qui perce dans les résultats."

Hueppe (1886, p. 38) points out that pleomorphism and variability of the cell form should be kept entirely separate. *Rodet,* on the other hand, in his book entitled "La Variabilité dans les Microbes" (1894, p. 38), speaks of "pléomorphisme" when temporary, of "variation" when constant variations of the form are observed. The occurrence of involution forms is characterized by him (p. 39) as "pléomorphisme monstrueux ou morbide." In *Pringsheim's* book on "Variabilität niederer Organismen" (1910, p. 25) pleomorphism is taken as part of morphological variability in about the same manner as advocated by *Migula.*

Considering such inconsistencies and differences of opinion, it seems best to use—at least at the present time—the term pleomorphism in the common though somewhat loose sense, merely indicating that various cell forms have been observed with one or the other species of bacteria. In face of the unsatisfactory situation of the whole problem it seems useless to ascribe to the term a sharply defined meaning, while in too many cases we have not yet secured the correct interpretation of the facts observed.

When explaining an apparent or a real pleomorphism of a bacterium one or the other or several of the following possibilities will have to be taken under consideration:

(1) Contamination.
(2) Incorrect classification of the pleomorphous organism among the bacteria.
(3) Presence of abnormal ("involution") forms.
(4) Occurrence of variations and of mutations.
(5) The normal development of different forms in the various stages of the complete life cycle of a species.

(1) CONTAMINATION.

To *Gaffky* (1881), as to many other followers of *R. Koch*, every change of a culture in form or virulence was an indisputable proof of "contamination." Of course, in many cases this suspicion was and will be fairly well founded, and the practical aims of the bulk of bacteriological work done will often justify a speedy discarding of such cultures without further test. However, as far as scientific investigations come into view, this widespread practice should not be followed too readily. At least in research laboratories the benevolent institution of the "suspended sentence" should be granted in some cases. Already in 1885 *Gruber* quite correctly questioned the dogmatic standpoint taken by *R. Koch* and his pupils, asking:

Muss man wirklich sobald man eine Aenderung der gezüchteten Bacterien wahrnimmt . . . die unreine Kultur fortwerfen?

Our own studies upon the life cycles of the bacteria started originally from two apparently contaminated cultures of Azotobacter (*Löhnis* and *Hanzawa*, 1914). And it is hoped that this review of the literature will help to stimulate a somewhat more cautious and more scientific treatment of this special point whenever feasible.

Hort (1916 *a*) says that the neglect of bacterial morphology has "led many a worker to assume that perfectly genuine examples of pleomorphic activity are merely examples of contamination," and "a careful scrutiny of alleged contaminations is absolutely fundamental."

When *Winogradsky* (1888) contested *Zopf's* (1881–1885) standpoint concerning the sulphur bacteria, he, like *Zopf*, drew his conclusions from mixed cultures, wherein he, like *Zopf*, saw all kinds of different and intermediate forms. But he did not hesitate to declare all these to be different species, and the monomorphistic view prevalent at that time did neither ask for proofs, nor did it pay any adequate attention to *Zopf's* answer (1895), which hardly ever has been quoted.

When *Gasperini* (1889) first studied the pleomorphism of the Actinomycetes (*Streptothrix Foersteri*), the preparates made up of coccoid forms, short and long rods, threads and screws, appeared to him like "une culture de bactéries fortement impure," and the interesting *Actinomyces* (Cladothrix) *asteroides* found by *Eppinger* (1890) in a case of pseudotuberculosis (cladothrichica) was at first thrown away as contamination. *Kitt* (1897–1898) discarded as "contamination" the Streptothrix growth which he obtained in virulent cultures of *B. erysipelatos suum.* No word is said about an adequate test, and analogous results secured by *Rosenbach* (1909) make it indeed very probable that also here the facts were vanquished by the theory. *H. U. Williams* (1912) isolated from a case of tuberculous pericarditis a spore-forming bacillus and a "Streptothrix," also spore-forming. Only after years a "separation" could be achieved, and then the bacillus frequently became so similar to the "Streptothrix" that the author further remained in doubt whether both are really different species or only stages of one organism. When I (1905 *a*) first studied the various morphological changes of *B. pneumoniae*, *lactis viscosum*, *radiobacter*, and *radicicola*, it also took some time before I was satisfied that all these alterations were indeed not the result of contamination. The close parallelism of the results obtained with the various cultures helped much to solve the problem.

With the Coryne- and Mycobacteria such puzzling cases are especially frequent. To *Spirig* (1903) we owe a thorough discussion of these questions as relating to the diphtheria organism. A "contamination" with a "Streptothrix," first (1899) considered by him to be a type of growth of the diphtheria bacillus, led to a close study of the subject (1903, p. 443). *Duval* (1914), like *G. A. Hansen* (1903), thinks that the lepra organism must invariably represent itself as a simple, constantly acid-fast bacillus. The now very numerous findings which strongly militate against this assumption had therefore to be discredited. The following quotation is very characteristic (*Duval*, 1914):

In the cases showing diphtheroids and streptothrical forms and acid-fast rods, the recognition of these as separate and distinct species, or the determination of any one or all of them as contaminators was often extremely difficult. So much so that in these cases the cultures were discarded.

Harris and *Wade* (1915) found diphtheroid organisms to be a rather common occurrence not only in and on the body, but also in air, water, etc. The strains isolated by them were

(apparently) quite constant. Accordingly, *Kedrowski's* very extensively studied leprosy cultures, as well as others of pleomorphous character, are declared to be mixtures of different organisms. *Bayon* (1915, p. 29) remarks very aptly that to discard in leprosy studies all diphtheroids because of their ubiquity—

would considerably simplify pathology. The microörganisms of syphilis, of tuberculosis, of cholera could also, on similar ground, simply be ruled out of court as far as their etiological significance is concerned.

The most recent studies upon the variations and mutations, shown by the bacteria, have helped to make one point clear, which is very important in this connection. As was probably first emphasized by *Firtsch* (1888), it does not infrequently happen that changes shown by some cells of a pure culture may persist for a more or less considerable length of time. Such cases naturally are most liable to be mistaken for contaminations. One of *Bernhardt's* publications (1915) furnishes interesting details relating to this point.

Usually, however, proper experimenting will soon succeed in bringing about such retrogressive changes which will settle the question. Otherwise, parallel tests will be very helpful. If they are incorporated in bacteriological routine work as they are used, e. g. by the chemist, the decision concerning presence or absence of contamination becomes not too difficult, provided, of course, that reliable methods are judiciously used.

(2) INCORRECT CLASSIFICATION OF PLEOMORPHOUS ORGANISMS AMONG THE BACTERIA.

The second possibility mentioned above, i. e. the assumption of an incorrect classification of an organism as a bacterium, has also been used quite extensively to eliminate pleomorphic organisms, rightly or wrongly.

F. Cohn (1872*b*, p. 139) stipulated that a bacterium can only multiply by fission. As true branching necessarily implies budding, it was declared by him never to occur with bacteria, despite the positive findings of *Dujardin* (1841) and *H. Hoffman* (1869), which were soon after confirmed by *Lister* (1873). The monomorphistic theory, as it developed on the foundation laid by *Cohn*, necessarily enhanced this stipulation. Undoubtedly true branching was often declared to be "false" branching, or if this was not feasible, the occurrence of branched forms was frequently considered to be sufficient reason to declare an organism a fungus, though it otherwise showed all characters of a genuine bacterium. The heavy weight of dogmatism is clearly demonstrated, e. g. in *Eppinger's* paper on his *Cladothrix asteroides*. As we know now, this organism is much inclined to exhibit true branching, and this was quite correctly described by *Eppinger* (1890) in the following manner, based on continuous microscopic observation: "A short thread first bends itself, a small granule becomes visible at this place, this develops into a little wart and further into a lateral sprout." Yet, curiously enough, the author calls this process a pseudo-ramification.

The tubercle bacilli were the first to show clearly true branching so frequently that it could not be simply discarded as "false." *Metchnikoff* (1888 *a*) separated them, therefore, from the bacilli and gave them the new name *Sclerothrix Kochii*. *F. Fischel* (1893) declared the tubercle bacilli to be the parasitic growth of a pleomorphic organism, probably belonging into a genus of higher fungi, an assumption which had been made before by *E. Klein* (1890) in regard to tubercle as well as to diphtheria bacilli. *Coppen-Jones* (1893–1896), who first was of the opinion that a special fungus accompanied the tubercle bacilli, later proposed the new genus name Tuberculomyces, and thought that also other pathogenic bacilli might be merely a type of growth of some higher fungi. *Conradi* (1900) declared the glanders bacillus to be a fungus, and wanted to have all bacteria which would show branching incorporated among the Hyphomycetes. *Levy* and *Klemperer* (1900), *Cornet* and *Meyer* (1903), *Jordan* (1909), *Carpano* (1913), and others took a similar standpoint. *Lehmann* and *Neumann* (1912) emphasize the many points which suggest a true natural relationship of the diphtheria, glanders, tubercle, and leprosy organisms, including their so-called pseudo forms, with the Actinomycetes, and consider the whole group either as a connecting link between bacteria and fungi, or as some lower Hyphomycetes.

The latter question has always been answered in a different manner. *Bollinger* (1877), *Gasperini* (1889), *Domec* (1892), *Lachner-Sandoval* (1898), *E. Levy* (1898), *Levy* and *Klemperer* (1900), *Neukirch* (1902), *A. Fischer* (1903), *Miehe* (1908), and others consider the Actinomycetes to be true fungi. *Kruse* (1896 *d*), on the other hand, says:

Es kann kaum einem Zweifel unterworfen sein, dass die Ähnlichkeit der Streptotrichen mit den Schimmelpilzen nur eine äusserliche ist, während sie den Bakterien nahe verwandt sind.

Meyerhof (1898), *Haas* (1905), *Peklo* (1910), and *Th. Cohn* (1913) also are not in favor of uniting Actinomycetes and fungi. *Bostroem* (1890) concludes from his extensive study of *Actinomyces hominis,* that this organism—though in the paper always called "Pilz" (fungus)—should be placed among the lower algae, next to *Cohn's* Cladothrix. Data concerning the reproductive organs, which will be discussed in Chapter II, indeed strongly indicate a natural relationship of Actinomyces, Cladothrix, and Crenothrix. *Günther* (1906), like *Fraenkel* (1891), still adheres to the older view, placing Cladothrix, Crenothrix, and Beggiatoa among the lower algae. *Zopf* (1881–1882), *Lachner-Sandoval* (1898), *A. Fischer* (1903), *Ellis* (1912), and others, however, prefer to accept them as higher or trichobacteria. The various facts concerning the formation and development of the reproductive organs (to be discussed in Chap. II) support this view.

When considering these problems it must be kept in mind that those characters which have been accepted for a long time as quite specific for the Actinomycetes and related organisms—viz., budding, branching, and apical growth—are by no means restricted to this particular group, but are quite common in all groups of the bacteria. This relationship is enhanced on the one side by the occurrence of motile stages within the life cycles of Actinomycetes and trichobacteria, on the other hand by a distinct similarity of the reproductive organs, formed by these organisms, as well as by the so-called true bacteria.

The fact that all bacteria show budding unquestionably militates somewhat against the time-honored conception of the "Schizomycetes," but it can not longer be justly disputed. Bacteria multiply in their vegetative state not only by fission but to some extent also by budding.[1]

That budding and fission are by no means so different as is usually emphasized in bacteriological textbooks had been already clearly pointed out by *Charles Darwin* (1868), who said (Vol. II, p. 430) that both are "essentially alike." They pass into each other almost imperceptibly. And he quotes *Huxley,* who wrote: "Fission is little more than a peculiar mode of budding."

The data collected in Table I (p. 17) showed that true branching has been actually observed with representatives of all groups of the bacteria. The smallest number of positive findings had to be recorded, quite naturally, with the cocci; but with these organisms distinct budding—the beginning of all true branching—has been found to be quite common. As early as in 1874 *Billroth* noticed that lactic acid streptococci exhibit occasionally "yeast-like branching" (p. 73). *Hueppe* (1891) thought that the budding forms which he found with cocci, rods, and threads, might indicate some relationship to Torula and Saccharomyces. *Kruse* and *Pansini* (1892), as well as *Adametz* (1895), brought further proof concerning the large yeast-like forms produced by streptococci. *Garnier* (1907) named one species explicitly *B. moniliformis.* The so-called bottle bacillus of *Unna,* though it usually grew in the form of a coccus of 1 μ diameter, and also showed culturally all marks of a genuine bacterium, has been removed by *Dold* (1909–1910) under the name of *Dermophyton Malassez* to a place between Hyphomycetes and Blastomycetes. *Meirowsky,* as well as *Kraus* (1913), are much inclined to see some "yeast" in it, on account of its budding. *E. de Negri* (1916) developed a similar culture of "Blastomycetes" (up to $5\frac{1}{2} \times 14$ μ) from a typical Corynebacterium. *Hort* (1917 *b*) placed the meningococcus among the Hemiascomycetes on account of its gemmation and multiple endosporulation. *Laurent* (1891) suspected the budding and branching nodule bacteria to be some form of a yeast or a Ustilago. The same assumption was made by *Calmette* (1893) in regard to a

[1] *Metchnikoff* (1888 *a*) wrote 30 years ago: "Aus den mitgeteilten Thatsachen kann man u. A. sehen, dass die Vermehrung durch Knospung der Familie der Bacteriaceen keineswegs so principiell abgeht, wie es gewöhnlich angenommen wird."

spirilliform organism found by him in cases of typhus, because it grew temporarily in a yeast-like form. And *Ferrán* (1885) saw in the cholera vibrio a type of growth of his so-called *Peronospora Barcinonae*.

The fact that probably all bacteria, especially all bacilli, show true branching has apparently first been pointed out by *Olsen* (1897), who was also of the opinion that bacteria represent some type of growth of Hyphomycetes. Exactly the opposite standpoint was taken by *E. Wolff* as late as in 1898. Even in the case of branching tubercle, diphtheria, and glanders bacilli he was inclined to see only a casual apposition of normal rods. *Gamaleia* (1900, p. 18) stated that all bacteria are able to produce branched forms; but no details are given. That he was right, however, is sufficiently proved by the facts collected in Table I (p. 17).

Lachner-Sandoval (1898, p. 20) thinks that it is "impossible" to classify an organism among the bacteria if it is able to exhibit true branching:

Die Unterbringung eines typisch verzweigten Organismus unter die Bakterien ist eine Unmöglichkeit.

If this standpoint would be generally accepted, no bacteria would be left at all, and all discussion upon their pleomorphism would become superfluous. However, I believe that there are important scientific, as well as practical, reasons to leave the bacteria in their present place.

Budding, branching, and apical growth alone are undoubtedly no sufficient reasons to advocate any change in their systematic position. In regard to the last-named fact it may be emphasized that apical growth has been always observed at least with all sporulating bacilli during their germination. A closer study of the growing bacteria, under less artificial conditions than customary, in all probability will reveal more interesting details in this respect.

It is not to be denied that these facts enhance to some extent the relations existing between bacteria and fungi. But the relations existing between bacteria, algae, and protozoa should not be overlooked. All bacteria are able to assume more or less the microscopical appearance of an Actinomyces. It has been pointed out why this organism will better take its place at the end of the bacteria, where their line leads over into the realm of the fungi, than among these organisms themselves. That branching occurs more often in young and vigorous than in old and weakened cultures has been shown by *F. Fischel* (1893), *Lubarsch* (1899), *Schulze* (1899), *Migula* (1900), *Concetti* (1901), *Lepeschkin* (1904), *Heim* (1906), *Cappellani* (1911), and others. The opposite statement made by *Günther* (1906) can not be accepted as correct. This lends support to a hypothesis, proposed by *Claypole* (1913), that the Actinomycetes are "representing the ancestral type that gave rise to both the higher fungi and true bacteria."

It has been mentioned above and will be discussed more completely later that a rather close relationship between streptococci and diphtheroids becomes more and more apparent. While the latter in their Actinomyces-like growth approach the fungi, the former have always been considered to be a distinct indication of the relations between bacteria and algae (Nostocaceae). Azotobacter furnishes a similar case. In its typical form it resembles the Chroococcaceae very much. Its spore-forming growth, however, is like that of other bacilli, easily to be induced to assume themi croscopical appearance of an Actinomyces. Crenothrix, also, exhibits clearly this double relationship.

Motility, as well as the formation of endospores, may be taken, as has been done by *Hueppe* (1891) and others, as an indication of phylogenetic relations existing between bacilli and flagellates, and it is not to be denied that much of what has to be discussed in Chapters II–IV concerning other modes of bacterial reproduction is duplicated by analogous facts in the life history of protozoa. Cytological reasons, too, have been repeatedly mentioned in favor of relations connecting bacteria and protozoa. *H. L. Russell* (1892) obtained distinctly monad-like forms from typical rod forms of marine bacilli. Especially in the case of his *Bac. halophilus* (a small motile, asporogenous bacterium) he studied those transformations in the hanging drop successively. Most of the large forms were motile, and it seemed probable to him that monads occurring in the water, but not growing on artificial substrates, were merely types of growth of this bacillus. Fusiform bacilli and spirochaets have been claimed frequently by protozoologists, though also in this case the bacterial nature is well discernible.

On the other hand several resemblances of Schizosaccharomycetes and large bacilli have been pointed out by *Lepeschkin* (1903).

Taking all these facts under consideration, it seems well justified to retain the bacteria in their entirety in their present position, and not to advocate the removal of one species or the other on account of its being inclined to show true branching or another kind of distinct pleomorphism.

(3) ABNORMAL ("INVOLUTION") FORMS.

The third possibility of making pleomorphous bacteria agree with the monomorphistic theory is to declare all "illegitimate" forms to be involution forms, teratologic, crippled, hypertrophic, or otherwise abnormal growth. Only with due recognition of the more or less practical aims of most of the work done in bacteriology it becomes somewhat conceivable how it was possible that so very many unscientific statements have been made in regard to this point.

Lafar (1887, p. 34), *Gotschlich* (1903, p. 43), *Bergey* (1907), *Jordan* (1909, p. 55), and others have correctly emphasized that unusual forms should be termed involution forms only when their degenerate condition is clearly demonstrated by their growth, propagation, and motility, being nearly or completely at a standstill and their cell content usually showing vacuolization granulation, and reduced stainability. *A. Fischer* (1903, p. 47) states that real involution forms are either dying or dead.

Frequently, however, the term is more or less grossly misused. I mentioned that *Migula* (1904, p. 37), for instance, calls involution forms all forms which he considers to be abnormal irrespective of their origin and of their vitality. *Levy* and *Klemperer* (1900, p. 25), *Maassen* (1904), and others take a similar standpoint. *Maassen* enumerates among the causes leading to "teratologic" growth: High or low temperature, liquid or dry condition of the substrates, their reaction, the stimulative effect of large amounts of carbohydrates, and of various salts. He points out specifically that those of the pathogenic organisms are also to be found in the host, sometimes just "when the bacterial development is at its height."

While *H. L. Russell* (1892, p. 194) correctly stated that the big globular forms which he found in old cultures of *B. granulosus* could not, despite this fact, be termed involution forms because they still were multiplying and forming spores, other authors do not hesitate to see "involution" forms even in quite fresh cultures, in spite of the full vitality of these cells. *Ravenel* (1896, p. 30) registered "involution forms" with his *B. cinctus* in cultures 18–20 hours old. Nothing is said about their appearance and behavior. *A. Fischer* (1897, p. 94) made the absurd demand that morphological and cytological studies of the bacteria should never be made with cultures older than 24 hours, because these "do not feel well" after this time:

> Man sollte über einen Tag alte Kulturen niemals zu Studien über den Bau der Bakterien verwenden, da schon nach dieser Zeit . . . die Bakterien anfangen, sich übel zu befinden.

M. Jones (1905) found that "evidence of degeneration" was "conspicuous" with the organism studied after 24–48 hours. But the author also reports that the colonies were only 1–1.5 mm. in diameter after 48 hours, and 5 mm. after 5 days. *Frost* and *McCampbell* (1910, p. 26) state when discussing the involution forms:

> Too rapid reproduction may cause aberrant shapes among some species.

Plotz, *Olitzky*, and *Baehr* (1915) say that in the cultures of the anaerobic bacillus, which they isolated from typhus exanthematicus, "degeneration and involution forms appear early, so that after repeated transplants the organism may assume a different appearance." *McFarland* (1916, p. 411) goes even so far to assume in regard to the enlarged and clubbed forms of the diphtheria bacillus:

> These probably represent an involution form of the organism, for (!) they are present in perfectly fresh cultures . . . The involution of the diphtheria bacillus seems to occur in proportion to the rapidity of its growth.

Accordingly, he finds the "involution," i. e. degenerate forms, prevalent on good substrates, whereas bad substrates furnished him only "short spindle and lancet shapes."

That, in fact, branched and clubbed forms of the tubercle and diphtheria bacilli are not involution forms has been pointed out in 1890 by *E. Klein*, who apparently was the first to

emphasize the now well-confirmed fact that they are to be found in young cultures as well as in the body. Similar statements have been made more recently in regard to *B. tuberculosis* by *Wolbach* and *Ernst* (1903), in regard to *B. mallei* and *B. diphtheriae* by *Hiss* and *Zinsser* (1914, p. 19), though in the latter case an accompanying picture (fig. 6) still bears the legend "degeneration forms" of *B. diphtheriae.*

Bongert (1901), *Gotschlich* (1903, p. 38), *Kolle* and *Hetsch* (1911, p. 24) accept branching and club formation as a normal stage of growth, whereas *Schmidt* and *Weis* (1902, p. 82), *A. Fischer* (1903, p. 49), *Abbott* and *Gildersleeve* (1903) take the opposite standpoint. The last-named authors do this especially because such forms were not seen regularly on "standard" media. *Migula* (1900, Vol. II, pp. 495, 499) thinks that a priori all branched forms of *B. tuberculosis* and of *B. diphtheriae* are to be considered "involution" forms and "degenerate"[1]). Accordingly, he (*Migula*, 1904, p. 38) declares the swollen and branched forms of *B. radicicola* to be "undoubtedly" involution forms. To *Stefan* (1906) it was even quite certain that they are pathologic. Also *E. F. Smith* (Vol. II, 1911, p. 114) believes that they are degeneration forms, because "such forms are either dead, or, if capable of further growth, return to the original form when placed on suitable media."

More than 30 years ago, however, *Prazmowski* (1888 *b*, 1890) found in the course of his thorough studies upon this organism that the so-called "bacteroids" appear when the development is at its height, and that they reproduce small rods. The latter fact had first been directly observed, 20 years earlier, by *Woronin* (1866), and it was afterwards confirmed by *Frank* (1890), later by *Hiltner* and *Störmer* (1903) and others. *Süchting* (1904) also noticed that "bacteroids" are abundant in the cultures when these are fully developed, whereas in cultures older than 8–14 days numerous small motile rods are present, originating from the branched forms. My own investigations (1905 *a*), as well as those of *Gage* (1910) and *Zipfel* (1911), confirmed and extended these findings. That according to *Morck* (1891), *Harrison* and *Barlow* (1907) the branched forms are prominently located in the growing, active part of the nodules, while in the youngest as well as in the oldest nodules only cocci and rods are present, agrees very well with the results obtained in cultures kept under suitable conditions. *Miehe* (1913), on the other hand, because he could not see further development of branched forms under the microscope, does not hesitate to call them "cripples" and all positive results recorded in the literature "fiction." But the normal rods of the organism used in these experiments (*B. foliicola*) also refused to grow under *Miehe's* microscope, and that his statement concerning the positive findings secured by other investigators is entirely unwarranted, goes without saying.

When *Hauser* (1885) first studied his pleomorphic Proteus, large globular, pear and club shaped forms (3–7μ) were described by him as "involution forms." But he pointed out himself that these very motile forms were already present, and sometimes even prevailed in the colonies when only a few days old, while they were replaced in old liquefied gelatine cultures by the small rods and cocci, characteristic of this group. By direct reinoculation the "involution" forms could be stabilized, so that they reproduced themselves, e. g., in 30 successive transfers, made during seven months.

The well-known "involution" forms of the plague bacillus, which are still virulent, appear in artificial culture within a few days, while again in really old cultures the small "normal" forms alone are present, as has been shown especially by *Albrecht* and *Ghon* (1900). In accordance with this fact, the same forms have been found by *Sata* (1900), *Dieudonné* (1903), and others in the body, showing full vitality and virulence. *Galli-Valerio* (1903) states explicitly that the various forms of *B. pestis* (globules, clubs, threads, branched cells, etc.) are not involution but evolution forms, because they appear first and the short rods later.

The meningococcus produces its "degenerate" giant forms in large numbers in only two days old cultures (*Kutscher* 1907). *Micrococcus melitensis* grows, according to *Eyre* (1907), in bacillary form only in old cultures or when the reaction of the substrate is not right, while

[1] In his own words (l. c., p. 499): "Dass diese Verzweigungen ebenso wie bei zahlreichen anderen Bakterien nichts weiter als Involutionsformen sind, braucht wohl nicht erst besonders hervorgehoben zu werden."

Saisawa (1911) found the rods in young, the cocci in old cultures. *Durham* (1898) has demonstrated that merely a change in the temperature suffices to turn the cocci into bacilli or vice versa; both are equally vital. *Jordan* (1916, p. 416), accepting the rod form as the normal type, calls the organism *Bac. melitensis*. *Kruse* and *Pansini* (1892) were not inclined to think that the rod-like cells produced by pneumo- and streptococci are involution forms, for they were found to be the result of an especially luxuriant development of the cultures. The large yeast-like cells of *Streptococcus lanceolatus* were found by *Axelrad* (1903) in young colonies on the plate.

That the large swollen forms produced by acetic-acid bacteria are not properly termed "involution" forms had been pointed out by *E. Chr. Hansen* as early as in 1879, and it was recently confirmed in the course of detailed studies by *Janke* (1916). *Bordoni-Uffreduzzi* (1888 *b*) said the same concerning the large globular, spindle-shaped and triangular forms occurring in cultures of his *Proteus hominis*. He sees in them an expression of luxuriant growth. Old and weakened cultures showed only the small "normal" rod-like cells. With the ozaena bacillus—another member of the *B. pneumoniae group*—*Simoni* (1900) got analogous results. And these were further confirmed by my own experiments with various nitrogen-fixing strains of the *B. pneumoniae* group (1905 *a*), which shed some interesting light on the relations existing between *B. radicicola, radiobacter*, and *pneumoniae*.

B. Chauvoei is another example of conspicuous pleomorphism. Its characteristic forms occur everywhere, in the cultures as well as in the tissue. But they, too, have been declared by *Fraenkel* and *Pfeiffer* (1895, legend to fig. 60, Pl. XXX) to be degenerate, crippled involution forms, merely because they are entirely unlike the typical cells which "obey the rule" of the monomorphistic dogma.[1]

In their interesting studies upon the morphology of the tetanus bacillus *Kanthack* and *Connell* (1897) correctly emphasize that the branching, club formation and mycelial growth shown by this organism can not be set aside as "involution forms", because they appear in the cultures when 18–24 hours old, and they disappear with increasing age.

The multitude of monstrous forms found by *B. Fischer* (1894, p. 36) to be characteristic for his *Halibacterium polymorphum* becomes visible in cultures not older than 2–3 days, when grown on most suitable substrates.

Baumgarten (1890) called the attention of cholera investigators to the important rôle which the so-called involution and degeneration forms of *V. cholerae* may play in cultures, as well as in the body. *Hammerl* (1906) and *Popoff-Tscherkasky* (1914) have furnished convincing proof that in this case, also, those terms have been greatly misused. All these globular, triangular, spindle-shaped and ramified forms were found to be very motile, abundant, and sometimes even exclusively present in young cultures; they could be propagated as such for weeks and months, and produced again "typical" commas and spirilla. Of special importance, however, is the fact demonstrated by *Bittrolff* (1912) that great variation may be shown in this respect by different strains, especially in the animal test.

Severin (1897, p. 513) wrote in regard to the characteristic triangular branched cells of his *Vibrio denitrificans:*

> Es kann kaum bezweifelt werden, dass wir es hier nicht mit Involutionsformen zu tun haben, erstens finden sie sich nicht in alten Kulturen, sondern im Gegenteil nur in frischen, und . . . derartige Formen färben sich sehr gut und weit gleichmässiger als die Mehrzahl der sich nicht verzweigenden Formen und besonders der Spirillen.

Reichenbach (1901) took the same standpoint concerning *Spirillum rubrum*, and *Bajardi* (1903) obtained branching so frequently in young cultures of *Vibrio lingualis Weibel*. that he thought this organism should be transferred to the Actinomycetes as "*Streptothrix lingualis*."

Spirochaeta pallida is, according to *Sobernheim* (1907), equally inclined to exhibit "atypical" and "involution" forms within the tissue. And the same holds true in regard to different species which are pathogenic to plants, as has been recorded by *Macchiatti* (1898) and *E. F.*

[1] "Sehr auffallend ist die ausgesprochene Neigung des Rauschbrandbacillus zur Bildung von Involutionsformen. ma ihm auch begegnen mag, im Gewebssaft der Tiere, in Bouillon, Gelatine oder Agar, fast stets trifft man zahlreiche, wunderlich verzerrt Misswüchse, degenerierte Zellen an, deren verkrüppelte Gestalt kaum noch eine Spur von Ähnlichkeit mit den typischen, vorschriftsmässigen Gliedern besitzt."

Smith (1911, Vol. II, pp. 73, 256, 288). The former author says concerning his *Bacillus Baccarinii* (the causative agent of the "mal nero" of grapevine):

Die Grösse wie auch die Gestalt dieses Bacillus variieren sehr . . . hier haben wir also einen schönen Fall von Polymorphismus; . . . die verschiedenen Gestalten folgen auf einander, wenn die Mikrobien über günstige Entwicklungsverhältnisse verfügen.

More details to be found on the following pages will amply support the conclusion, which can be drawn from the cases discussed, viz., wherever the so-called involution forms have been made the object of more discriminate studies, nearly invariably it has turned out that it was a mistake to presume their being degenerate, merely on account of their "atypical" appearance. Actually, in many cases they have shown themselves to be constantly occurring stages in the life history of the bacteria. The "typical"—not the so-called involution—forms have been often found to prevail in old cultures, whereas the "atypical" forms were predominant when the development was at its height. *Wasserzug* remarked in 1888 (*b*) that involution forms were sometimes more normally visible than the so-called normal forms. And still earlier *Finkler* and *Prior* (1885) emphasized correctly that it is usually by no means easy to decide definitely whether morphological changes of the bacteria—the so-called involution forms—are to be considered pathologic or normal occurrences within their life history.[1]

The distinctly unscientific trend of opinion, which has been promulgated in this respect by some of *R. Koch's* overenthusiastic pupils, is clearly substantiated by the following quotation, taken from *C. Fraenkel's* "Grundriss der Bakterienkunde" (1891, p. 10). The involution forms, says he—

gehören nicht in den Entwicklungsgang der betreffenden Bakterienart, sie sind kein notwendiges, unentbehrliches Stück des Weges, welches das einzelne Individuum von Anfang bis zu Ende durchmisst, und verlieren damit den Anspruch auf Legitimität, sind uns nichts weiter als ein Anzeichen dafür, dass unter dem Einflusse ungünstiger Verhältnisse eine Degeneration des Bakterienprotoplasmas stattgefunden hat.

Yet this standpoint has been fully shared by authors like *Macé* (1897, p. 323). *A. Fischer* (1903, p. 49), *Maassen* (1904), *Günther* (1906, p. 22), and others.

The real value of *Fraenkel's* reasoning becomes quite evident when we consider the following two points: In all cases, where purely vegetative propagation is successful, as with all lower, as well as with many higher, plants, all reproductive organs, flowers and fruits, are entirely "unnecessary," can not be accepted as "legitimate" and must be considered as indicating degeneration, because the vegetative growth comes to a standstill at this time. Further *Fraenkel* admits that *B. anthracis* (like many other bacilli) also produces coccoid forms. But he is absolutely certain that these do not form a part of the life cycle of the bacillus, "because" they either do not grow at all, or if they do, they produce again the "regular, typical" rods, i. e. they behave like spores.[2]) The endospores had been studied by *R. Koch*, while other reproductive organs remained unknown to him. Therefore, to *Fraenkel* and to other faithful adherents the former are of greatest importance and the latter entirely "illegitimate."

A comparison of the so-called involution forms with the endospores is of special interest. *Duclaux* observed several decades ago (1883, p. 654) that his *Tyrothrix virgula* and *scaber* produced characteristic swollen forms, resembling spermatozoids, but that only later, within these swellings, the endospores appeared. Our *Bac. malabarensis* (*Löhnis* and *Pillai*, 1907) behaved in exactly the same manner. *Braem* (1889) made some interesting experiments which clearly show that inoculation into water is as useful to stimulate the appearance of the so-called involution forms as it is to induce spore formation. *A. Meyer* (1901 *a*) points out that also branching occurs at an earlier stage of growth than spore formation; and *Heymann* (1903) obtained

[1] "Wir halten es für ausserordentlich schwierig, sichere Beweise dafür liefern zu können, wo die Grenze liegt zwischen den mannigfachen Variationen der Form, welche als pathologische Zustände der Vibrionen aufzufassen sind, einerseits, und andrerseits solchen Bildungen, welche als physiologische Entwicklungszustände angesprochen werden müssen."

[2] In *Fränkel's* own words (l. c., p. 9): "Gehören nun derartige 'Kokken' in den Entwicklungskreis der Milzbrandbacillen? Gans gewiss nicht. Denn . . . dieselben sind entweder überhaupt nicht mehr fortpflanzungsfähig . . . oder aber sie lassen sogleich wieder die . . . typische Wuchsform, das Langstäbchen von regelmässiger Gestalt aus sich hervorgehen. Es sind diese Gebilde eben nur der Ausdruck für eine stattgefundene Entartung der betreffenden Bakterien, es sind Degenerations- oder . . . Involutionsformen, Misswüchse, die für die Beurteilung des normalen Wachstums gar nicht in Betracht kommen können."

analogous results concerning the "involution" forms of diphtheria bacilli and the (later) appearance of the granules in them giving *Neisser's* staining reaction.

Endospore formation and Neisser reaction have been always accepted by the followers of *R. Koch* as of very great systematic and diagnostic importance. Therefore, the adverse valuation of the "involution" forms, as taught by them, is by no means in accordance with the facts. It would be even more correct to call the endospores involution forms, because they are to be found in old cultures, when motility and vegetative propagation is at a standstill. It is true, some of them, though not all, will produce new rods when transferred to a new substrate. But many of the so-called involution forms act in the same manner, and just this was the reason why several authors discarded them as being of no interest or importance.

Some authors, like *Kruse* (1896 *a*, pp. 61–64), *W. Winkler* (1899), *Gamaleia* (1900), *Fuhrmann* (1906), *Taddei* (1909), *Löhnis* (1913, p. 24) and *Ambrož* (1915), have advocated a closer study of and a more scientific attitude against the so-called involution forms. That their appearance is dependent on external (chemical and physical), as well as on internal (biological) influences, is clearly indicated by the interesting results secured by *Gamaleia* (1900), *Matzuschita* (1900), *Rosenfeld* (1901), *Maassen* (1904), *Péju* and *Rajat* (1906), *Hata* (1908), and *Taddei* (1909), on substrates containing various salts, relatively large amounts of carbohydrates, or possessing an unusual reaction. *Kruse* (1910, p. 8) points out that a special stimulation of growth is frequently responsible for their appearance, whereas *A. Meyer* (1901 *a*) emphasizes that undoubtedly "inner reasons" are the more important ones, because those forms often develop more or less irrespective of substrate, temperature, etc. Accordingly, some species are very much inclined to produce such special growth, while others under analogous conditions show little or no alteration at all (*Migula*, 1897, Vol. I, p. 52). *Fuhrmann* (1908) found, in accordance with *Matzuschita* (1900) that moderate salt concentration merely accelerates the normal growth, while high concentrations, of course, act detrimentally or may eventually cause the death of the cells.

If the vitality of so-called involution forms is not tested very carefully, it may easily happen that incorrect results are recorded. The uniformity of the methods usually employed is liable to cause misleading observations. The difficulties, which have often arisen when new species had to be isolated, should be kept in mind. That a marked periodicity in the progress of cell growth may often become noticeable, when tested on the ordinary substrates, has been demonstrated with pyogenic staphylococci and with dysentery bacilli by *Reimer* (1909) and with diphtheria bacilli by *Springer* (1913). The initial increase only lasts a few days, then (apparently) a reduction takes place, followed again by another maximum, and eventually by more of such waves. The following examples from the last-named author's paper (in round figures and abridged) may elucidate this point:

Germs per cc.	Experiment No. 4.	Experiment No. 5.
At the beginning	3, 800	4, 176
After 4 days	33, 000, 000	14, 000, 000
After 8 days	1, 000, 000	4, 600, 000
After 22 days	23, 000, 000	46, 000, 000
After 42 days	19, 000, 000	366, 000, 000
After 62 days	63, 000, 000	20, 000, 000

It would be well worth while to combine such experiments with a close study of the appearance and disappearance of the "involution" forms. It can hardly be questioned, that such investigations would greatly help to modify the prevalent theories concerning the meaning and importance of the different types of bacterial growth.

Looking back upon all those conflicting and often very incongruous statements, which have been made by the bacteriological writers during four decades, one might feel much inclined to agree with *Fokker*, who said as early as 1888 (p. 125) that the term "involution form" is only "a name without any significance." It would be best to drop the term entirely. As this, however, in all probability will not be done, it might be advocated to use the word at least

exclusively in its correct sense. Webster's New International Dictionary (1910) contains the following explanations:

Involution = retrograde development or retrograde evolution; degeneration.

Degeneration = a progressive deterioration, as a return to a simpler and less highly organized condition in the evolution.

Accordingly, it would be quite correct to call involution forms the small "normal" forms, which in really old cultures often replace the larger, more highly organized cell types, which have so far been termed involution forms, evidently without sufficient reason. But such practice would only lead to still more confusion. All that can be expected in the future seems to be a somewhat more cautious use of this greatly overworked expression. Specialized studies of the subject would prove very helpful in this respect.

(4) VARIATIONS AND MUTATIONS.

The fourth explanation, which has to be taken under consideration in regard to apparent or true pleomorphism among the bacteria, is the occurrence of temporary, as well as of more or less permanent, changes in the type of growth, called adaptation, modification, variation and mutation. Again much differences of opinion are to be found in the literature concerning the correct use of these expressions. This point has been discussed in the publications of *Pringsheim* (1910), *Nyberg* (1912), *Dobell* (1913), *Toenniessen* (1913), *Jollos* (1914), *Jordan* (1915), and of *Prell* (1917).

For our purposes it will suffice to use preferably the general term "variability," as in practically all cases observed so far, quite naturally cause as well as stability (or instability) of the occurring changes have remained more or less in doubt. In some cases the influence of external conditions and the instability of the change induced by them are evident, in other cases the opposite holds true. How a change of substrate may influence the form of the bacteria has been clearly demonstrated, e. g., by *Wasserzug* as early as 1888. By studies upon the variability of the streptococci, *Lemoine* (1896) was led to the conclusion that not only the influence of the substrate had to be considered, but also the "modifications subies au sein même de l'organisme." *Neumann's* (1897) investigations upon the variability of pigmentation of the micrococci still more indicated a predominance of internal against external causes. *Luckhardt* (1901), *Rettger* and *Sherrick* (1911), *Jordan* (1915), and others have furnished more examples in this direction. That, on the other hand, external conditions occasionally may assume very great importance has been exemplified, e. g., by *Bordet* and *Sleeswyk* (1910) concerning the change of agglutinability in various species, by *Geisse* (1914) in regard to the pathogenicity of saprophytic staphylococci, by *Heinemann* (1915) in regard to pathogenicity and morphology of *Streptococcus lactis*, and by *Bernhardt* (1915) with *B. typhi, dipthheriae*, and others.

With some of the variants obtained in these experiments considerable stability has been recorded. *Hill* (1899) isolated a strain of *B. diphtheriae* which showed branching very persistently. *Lepeschkin* (1904) also succeded in splitting off an equally inclined strain of his *B. Berestnewi*, making use of single-cell cultures. *Barber* (1907), too, obtained from single cells strains possessing morphological peculiarities which were (apparently) constant. Whether the constancy of a new character is in fact real or apparent must necessarily remain in doubt in many cases. For instance, a white Micrococcus strain isolated by *Neumann* grew white for six years and returned then to the original yellow type. One of *Luckhardt's* white Prodigiosus cultures became suddenly red after several months' experimenting, only to return to white afterwards. One of my own stock cultures, a brown variety of *B. fluorescens*, became entirely white after it had been kept for about two years in the collection, always being transferred in approximately three months intervals to beef agar made up in the same manner. The next inoculation produced the brilliant green of a typical Fluorescens, but the next one was brown again, and so it remained through several years. As most observations naturally must be of much shorter duration, the question concerning the stability of a new form will always remain more or less in doubt. It is well known that frequent transfers to the same substrate repeated after

a few days tend to keep a strain constant, whereas older cultures are much more liable to furnish either new variants or to exhibit atavistic tendencies. *Fürst* (1914), e. g., who studied anew and in single-cell cultures the remarkable variability of the Finkler-Prior vibrio, first investigated in mass cultures by *Firtsch* (1888), obtained constant variants when these were transplanted after 5–6 days, whereas by 2½–4 months' intervals the number of atavistic changes was increased, and 4-months-old cultures produced again a growth exhibiting the normal original characters. *Burckhardt* (1914) was able to restore motility in some immotile stock cultures of *B. coli* not by frequent transfers, but by starting from very old material. Immotile strains, on the other hand, could be easily obtained by keeping them under less suitable conditions. These facts are in good agreement with some observations mentioned above concerning the so-called involution forms; we will have to refer to them when discussing the various changes occurring in the different phases of the life cycles of the bacteria.

While the doctrine of constancy, as promoted by *R. Koch* and his pupils, was rather short-lived as far as the *function* of the bacteria comes into view, it has found, on the other hand, up to the present time considerable support in regard to the *form* exhibited by this special group of organisms. As Life, however, is characterized, according to *Spencer*, by the "continuous adjustment of internal relations to external relations," it is, indeed, self-evident that variations *must* occur under changed conditions (*Spencer*, 1898, p. 334). That *all*, morphological as well as physiological, characters of the bacteria may vary has been explicitly stated, probably for the first time, by *Nägeli* (1882, p. 135). The following of his sentences (p. 138) is remarkably accurate when we consider that it was written more than 35 years ago:

> Die Species wird nicht durch absolute Merkmale kenntlich sein, sondern dadurch, dass sie unter bestimmten äusseren Umständen bestimmte Modificationen des morphologischen und physiologischen Verhaltens, unter anderen Umständen andere Modificationen zeigt.

Ziegler (1885, p. 203) also admitted that variability occurs "within definite limits," though it had been more correct to say "indefinite" limits, as he expresses himself as follows:

> As to the extent of the cycle of variations, through which any one of the known bacteria may pass, we know indeed but little.

Among the German and Austrian bacteriologists it was especially *Escherich* (1894), *Hueppe* (1896), *Kruse* (1896, 1910), and *Lehmann* and *Neumann* (1912), who have insisted upon an adequate study of these problems and have done much in reducing the chaos in systematic bacteriology caused by the widespread habit to incorporate into the literature many badly studied instable varieties as constant species. Even *Migula*, who at first was one of the most ardent supporters of the latter practice, had to admit later (1904, p. 35) that several organisms, e. g., the cholera vibrio, are characterized by a very great variability.[1]

Among the French authors *Macé* (1897) takes a distinctly contradictory standpoint, similar to his position in regard to the pleomorphic character of the bacteria. On the one side he says (p. 323):

> On peut affirmer à l'heure présente, avec la probabilité la plus grande, qu'il existe chez les bactéries des espèces vraies, à charactères fixes, se produisant et se perpétuant sans varier.

But only a few pages further on we are informed (p. 329):

> D'une autre côté, il n'est guère possible d'admettre une fixité absolue des charactères que l'on considère comme specifiques. De nombreux exemples preuvent, au contraire, qu'à côté des charactères physiologiques que nous savons variables, les caractères morphologiques eux-mêmes ne nous montrent pas une fixité absolue.

Otherwise, all French bacteriologists are accepting unanimously the variability of the bacteria as a necessary correlative to their pleomorphism, as has already been shown by some of the quotations given above. The following paragraph taken from *Duclaux's* "Traité de Microbiologie" (1898, p. 605) may serve as another characteristic example:

> A ces variations de fonctions viennent se supposer des variations de formes au sujet desquelles les savants avaient fort discuté, les uns soutenant qu'elles étaient assez constantes pour entrer dans la diagnose de l'espèces, les autres

[1] "So zeigt besonders der Organismus der asiatischen Cholera eine ausserordentlich grosse Zahl von Varietäten, die von stark gekrümmten bis fast geraden, von sehr kurzen bis sehr lang gestreckten Zellen fast alle Zwischenformen zeigen und sich dabei in Kulturen auffallend konstant gezeigt haben . . . Diese Varietäten behalten auch auf verschiedenen Nährböden ihre Formen bei, sind also keine 'Ernährungsmodifikationen,' und sie würden, bei unserer gegenwärtig sehr unsicheren Kenntnis von der Umgrenzung naturhistorischer Arten bei den Bakterien, sicher als verschiedene Arten betrachtet werden, wenn sie nicht eben als Erreger derselben Krankheit gefunden wären."

qu'elles étaient indéfinies. On voyait bien maintenant que cette question n'en était pas une, ou plutôt qu'elle disparaissait derrière la question plus grosse et plus profonde des variations de la fonction protoplasmique . . . Bref, a l'idée de spécificité, encore dominante il y a dix ans . . . s'en est substituée une autre, . . . celle de la plasticité de la fonction protoplasmique.

More recently, *LeBlaye* and *Guggenheim* (1914, p. 12) have strongly emphasized the very great variability exhibited by most of the species, which are forming groups of more or less atypical "races."

Among the British authors, it was especially *Adami* who has repeatedly (1892–1916) called the attention of his fellow-bacteriologists to this important problem. In his second paper on this subject (1894) he pointed out that experimentally changes can be produced which would be considered a priori as characteristics of a totally different species, and that on account of the wide variability to be observed under different conditions "the first step must be in the direction of the establishment of a system of broad groups."

In the American literature some discussions upon the variability of the form of the bacteria are to be found in the works published by *Chester* (1901), *Park* and *Williams* (1914), and others. However, as has been illustrated by the quotations given above, the doctrine of simplicity and constancy of the form has been supported by many of the American bacteriologists until quite recently. Moreover, there is even a tendency now to establish not only species, but genera on some biological characters, though the still greater variability of these marks, clearly indicated in the early publications of the French authors (*Guignard* and *Charrin*, *Wasserzug* and others), has been so often confirmed since then that it is now well beyond question. *C.-E. Winslow* and *A. Rogers-Winslow* (*1908*), e. g., have advocated dividing the micrococci into different genera mainly on the basis of their pathogenicity and pigment-production. The systematic relationship of the streptococci, too, should be established, according to the first-named author (*Winslow*, 1912), on the outcome of biometric studies of their fermentative powers, a method which had been advocated, though only for practical purposes, by *Andrewes* (1906) and other British authors. That these very variable properties can not be used for classification has been demonstrated anew by *Broadhurst* (1915) in regard to the streptococci, and by *Burton* and *Rettger* (1917) for the Colon-Aerogenes group. *Kligler* (1913), on the other hand, fully confirms the correctness of *Winslow's* standpoint and claims that there is "a remarkable general correlation between pigment production and other properties." However, white cocci sent to the collection used for these studies were found by *Kligler* to be orange. An organism, originally exhibiting all characters of *Micr. agilis*, was declared by him to be either *M. citreus* or *roseus*, indicating beyond doubt that also in this case the generally observed instability of the physiological properties has exerted its influence.

Numerous papers have been published during the last 10 years, mostly in Europe, wherein the morphological as well as the physiological variability of some groups of bacteria have been more or less thoroughly discussed, usually under the aspect of mutations. This point was first emphasized in the publications of *M. Neisser* (1906), *Massini* (1907), *Penfold* (1911–1912), and *R. Müller* (1912) concerning lactose fermenting "mutants" of *B. coli*. The preliminary communication made by the first-named author was immediately followed by still more interesting remarks by *Schottelius* (1906) and *Gotschlich* (1906) concerning *B. pestis*, and by *Gruber* (1906) in regard to Finkler-Prior's vibrio. The so-called mutation of *B. pestis* has been further studied by *Markl* (1914). *Toenniessen* (1913–1914) added important data upon the variability of *B. pneumoniae*. *Nyberg* (1912) succeeded in producing artificially with all of 140 strains of different lophothrichic bacteria (Fluorescens, Cyanogenes, etc.) those different types of colonies which have been observed in many other investigations on "mutations." *Baerthlein* (1911–1918) obtained them with cholera, typhoid, paratyphoid, dysentery, coli, and diphtheria bacilli, as well as with micrococci, *Bac. proteus* and *pyocyaneus*, and saw them always accompanied by considerable changes of the cell form. *Köhlisch* (1916–1918) and *Gildemeister* (1917) confirmed and extended *Baerthlein's* findings with regard to the Coli-Typhosus group. The great variability occurring in the diphtheria group has been elucidated to some extent by the investigations of *Ohlmacher* (1902), *Goodman* (1908), *Bernhardt* and *Paneth* (1913), and others. *Stamm*

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(1914), *Olsson* (1915), and *Feldmann* (1917) made the cholera vibrio the object of their studies. *P. Eisenberg* (1914–1918) worked with representatives of various groups of bacteria (*Bact. prodigiosum, violaceum, fluorescens, pneumoniae, typhi, coli, dysenteriae*, and *Sarcina tetragena*). However, it would be entirely without foundation to assert that the two foremost marks of true mutation, viz., the sudden appearance and the constancy of the alteration observed, had been sufficiently demonstrated in any or all of these cases. That there *may* have been some true mutation is not to be denied. But the examples given above indicate clearly, how difficult, nay even impossible, it will be to find out in the ordinary course of examination which only lasts some weeks or months, whether the change in fact is constant or not. And whether the new form or function has appeared gradually or indeed suddenly is a problem still more difficult to solve. Accordingly, several authors, like *J. Klein* (1912), *Bernhardt* (1912), *Berry* and *Banzhaf* (1912), *Saisawa* (1913), *Feldmann* (1917), and *Baerthlein* (1918), have emphasized that the alterations actually did not represent mutations, but only temporary adaptations, fluctuating variations or atavistic reactions. As older cultures generally are more inclined to produce aberrant strains, it has been repeatedly assumed that accumulated metabolic products are the foremost cause of the effect. To some extent this is undoubtedly true. But, as with the involution forms, it must be also kept in mind with regard to morphological and physiological variations shown by cultures of various age, first, that only some of them show variability and these again to a different degree, while others do not, and in the second place, that with increasing age of the culture there may be a complete return to the original, so-called typical, character.

Bernhardt (1915), *Olsson* (1915), and others have quite correctly spoken of the "cycle of variation" characteristic for every species or group of bacteria. This cyclic alteration of form and function is, indeed, an important attribute of the normal life cycles of the bacteria. And this fact easily explains, why in all cases more or less variability can be observed from the start, when a sufficiently large number of strains, belonging to one species, is isolated at the same time. Accumulation experiments, as recommended by *Beijerinck* (1898, 1901 *a*), are of very great importance in this respect. *Kruse* (1910, p. 1153) says:

Es ist von vornherein zu erwarten, dass die natürliche Züchtung in ähnlicher Weise Abarten erzeugen wird, wie die künstliche. Die Erfahrung hat das auch immer wieder bestätigt.

Grassberger (1905) was equally right when he wrote:

Darüber kann kein Zweifel bestehen, die Natur versteht das Variieren noch viel besser als wir, und auch das Misshandeln, speciell dort, wo es sich um die Wechselwirkung zwischen verschiedenen Organismen dreht.

Some authors have, therefore, strongly advocated to study freshly isolated strains, so as to avoid those "artificial" alterations caused by long continued growth on the substrates used for laboratory work. For instance, *LeBlaye* and *Guggenheim* (1914, p. 10) write:

Un diagnostic méthodique n'est possible que si l'on opère avec des cultures fraîchement retirées de l'habitat naturel. Ainsi se trouve éliminées les erreurs innombrables qui résulteraient des modifications que subissent les caractères morphologiques et biologiques des espèces sous l'influence du séjour dans les milieux artificiels.

On the other hand, the "standardization" not only of the methods to be applied, but of the bacteria themselves to the extent of eliminating all natural varieties, has been also recommended. *R. Koch's* pupils, the representatives of the extreme monomorphism, naturally took the leadership in this respect. *Fraenkel* (1891, p. 10) said:

Wenn man dafür sorgt, dass ein solches (i. e. apparently pleomorphic) Bakterium dauernd unter gleichmässig günstigen, unter den besten Ernährungs- und Wachstumsbedingungen steht, so bleiben die abnormen Formen aus, und wir bekommen einen einheitlichen, fest umschriebenen Eindruck von seinem äusseren Verhalten.

However, it is by no means certain, whether the ordinary standardized laboratory methods will afford the most suitable conditions of growth. In fact, another statement in *Fraenkel's* book (p. 132) explicitly admits that undoubtedly many microörganisms do not grow at all on the media commonly used, and—

Die Eintönigkeit des Verfahrens ist gewiss häufig die Ursache für das Fehlschlagen der Culturversuche.

Kruse (1896, p. 476; 1910, p. 1125) says:

Die Milzbrandbacillen von Maus auf Maus übertragen, das Essigbakterium immer frisch mit alkoholischer Nahrung gespeist, der Prodigiosus von Kartoffel auf Kartoffel übertragen, verändern sich nicht, so lange man auch das Experiment fortsetzt.

But as early as 1879 *E. Chr. Hansen* showed that the acetic acid bacteria in alcoholic fluids, where they grow best, are very much inclined to undergo conspicuous changes in their morphology, while they are "typical" small rods in the weakly growing layers on artificial substrates. The anthrax bacillus, on the other hand, will never show its very characteristic spore formation, when it is transferred in quick succession from mouse to mouse. But if we would follow the advice given by *A. Fischer* (1897) to study only 1-day-old cultures, then it would be indeed possible to get many uniform, though, of course, very incomplete, results.

McFarland's Textbook on Pathogenic Bacteria (1916) contains another statement of interest in this respect (p. 214):

While the appearances of the freshly isolated organism should be carefully noted, too much stress should not be laid upon them, and before beginning the systematic study of any new organism it should be made to grow for several successive generations upon two or three of the most important culture media. Its saprophitic existence being thus established, the characteristics manifested become the permanent peculiarities of the species.

Some doubt, however, will be justified whether it is, indeed, a correct scientific practice first to change artificially a parasitic organism, which naturally may be very little inclined to grow on our laboratory substrates, no matter how much "importance" we may attribute to them, so that it will assume a different, distinctly saprophitic character, eventually lose its pathogenicity more or less, and to conclude then that now "the characteristic peculiarities of the species" have been demonstrated. It seems, indeed, quite probable that the "domestication" of the bacteria will often alter their morphology, as well as their physiology, relatively to no less degree than it has been the case with the domesticated higher plants and animals.

How deeply the changes caused by continuous artificial cultivation may affect the general appearance of a strain is e. g. clearly reflected in the statement, made by *Migula* (1900) in the foreword to the second volume of his "System der Bakterien," saying that many of the cultures tested by him differed so widely from the original description that they were hardly recognizable. If the advice had been followed which was given by *Adami* (1894), viz., that all systematic studies should be continued not less than a year, and a second description of a so-called new species should be published 12 months after the first one in the same journal, the situation would be much better to-day in many directions. It needs hardly to be emphasized that such work as was done, for instance, by *Bredemann* (1909) with the Amylobacter group, where by persistent "training" of a large number of varieties a general species character is clearly brought out and made more or less permanent, will always undoubtedly have its great value. The peculiarities of aberrant strains, however, should also be carefully studied and recorded. This holds true especially as far as alterations of form and of function occur as the result of natural variability

(5) MORPHOLOGICAL CHANGES DURING THE LIFE CYCLE.

The fifth and last explanation, which eventually may help to solve some puzzling problem concerning bacterial pleomorphism, is the normal development of different forms in the various stages of the complete life cycle of a species.

So far, this point has met with but little consideration, though it will undoubtedly win in importance, as investigations go on. Some valuable material, however, is already available.

As mentioned before (pp. 30, 32), studies upon the variability of the bacteria have shown that, at least in some cases, a distinctly cyclic appearance and disappearance of the "variants" was quite evident. And as far as the so-called involution forms have been considered to be worth studying, the same fact has been noticed, viz. the original form first produces various "involution" forms, which later reproduce the "typical" form, so that eventually a several months' old culture again contains only "normal" cells. Numerous references have been given

on pages 24–28. At the latter place the investigations of *Riemer* (1909) and of *Springer* (1913) have been recorded, which clearly indicate that a distinct periodicity of bacterial growth is noticeable under suitable conditions. It may be added here that the result of our own studies upon the life cycle of the Azotobacter group (*Löhnis* and *Smith*, 1916 *a* and *b*) are in complete agreement with these findings. In soil as well as in nutrient solution a precise succession of the different characteristic stages in the development could be followed not only once, but repeatedly, without making any transfers or any other alteration than adding water aseptically, from time to time, when this became necessary.

The rather unnatural "overstuffed" substrates which are used most frequently in the laboratories will often interfere with such observations. Large amounts of metabolic products may kill the bacteria at an early date, and their presence has also often led to the assumption that they are the cause of the appearance of "variants" and "involution" forms. It is, of course, readily to be admitted that they, indeed, may have exerted some influence, and will often be able to do so. However, as the same or similar alterations are obtainable under quite different conditions, and a successive alternation of "degeneration" and "regeneration" can be easily established on suitable substrates, the natural tendency of the living cells themselves has also to be kept in mind. Moreover, it should not be overlooked that such changed forms, produced apparently under the influence of the metabolic products accumulated in the old substrate, not infrequently retain their peculiar shape very persistently through many transfers on fresh substrates.

In this respect some observations made by *Stamm* (1914) upon the variability of *Vibrio cholerae* are of great interest: 13 typical cultures were kept in water; 6 remained constant, 7 showed profound alterations, and these new forms remained again constant in more than 540 transfers made during 30 months, provided that the transfers were made frequently. Material taken from older cultures, however, either went back to the typical form, or showed further alteration. *Bernhardt* (1915) recorded analogous results with meningococci, typhoid, paratyphoid, septicaemia, and diphtheria bacilli. Daily transfers kept the "variants" obtained from old cultures constant for several generations. As has been demonstrated by *Preisz* (1904) and others, the so-called secondary colonies, frequent especially in old growth of spore-forming bacilli on agar, are also much inclined to produce rather constant strains of different morphological and physiological character. That giant growth and increased resistance of the cells are typical for this new development, is obviously not in accordance with the theory of the dominating influence of the accumulated metabolic products. The "tertiary" colonies, which sometimes develop after another interval, may be accepted as additional indication of the periodicity of growth occurring under suitable conditions.

That the pleomorphism of the bacteria is closely connected with their life cycle was already the opinion of some early French writers, like *Artigalas* (1885), *Cornil* and *Babes* (1890), and *Macé* (1897), who have been quoted on page 8. Two more references may be added here. *Billet* (1890, p. 208) stated that every organism studied by him exhibited "un cycle évolutif bien defini," and *Duclaux* (1898, p. 607) said:

Il faut prendre un microbe comme un être à générations alternantes multiples et variées, se succédant non suivant une formule regulière, mais suivant les conditions de l'ensemencement. Le lien de l'espèce, c'est la loi qui préside à chacun de ces changements, et la variété des formes et des fonctions n'est pas du tout en contradiction avec l'unite de l'espèce.

In England *Lankester* wrote as early as 1873:

The existence of true species of bacteria must be characterized . . . by the ensemble of their morphological and physiological properties as exhibited in their complete life histories.

The same standpoint has been taken later by several British authors like *H. M. Ward* (1892, 1910), *Crookshank* (1896), *Walker* and *Murray* (1904), *Dobell* (1911), *Young* (1914), and *Hort* (1915–1917). The changes observed by *Walker* and *Murray* in cultures of *B. typhi*, *coli* and *V. cholerae*, were accepted by them as signs of "an unexpected complexity in the life history of these microörganisms." *Dobell* wrote (1911, p. 484):

It appears to me probable that . . . the majority of bacteria may possess a wide range of variation in their outward form at different stages in their life histories.

Young emphasized that it is necessary "to try to obtain as many stages of each life history as possible." Of special importance, however, is the following statement made by *Hort* (1917*a*), because it is based on a broad experimental basis:

Evidence of complex bacterial life cycles is constantly before us, even in ordinary standardized laboratory media, though it may, and often does, require persistent looking for. The truth, in fact, appears to be that we have gone astray in this matter, because we have in the past invoked too easily the theories of contamination, of involution forms, nd of mutation, and have forgotten that the natural environment of bacteria, whether as saprophytes or as agents of disease, is in a perpetual state of flux.

In the older German literature the life cycles of the bacteria have been discussed, of course, more or less hypothetically, by those authors who like *Nägeli*, *Neelsen*, *Zopf*, and *Haberkorn*, tried to defend the polymorphistic standpoint against the strict monomorphism of *Cohn* and *Koch*. Some quotations were given on pages 11 and 13. *Nägeli* (1882) was undoubtedly right when he wrote:

Auf das leichte und subjectiv willkürliche Geschäft der beschreibenden Unterscheidung muss nun erst die eigentliche wissenschaftlich objective Arbeit der exacten experimentellen Untersuchung folgen (p. 139). Durch Züchtungen, die hinreichend lange unter den verschiedensten äusseren Umständen fortgesetzt werden, ist zu bestimmen, welche Formen sich in einander überführen lassen und welche nicht (p. 138).

The same holds true concerning the following statement made by *Zopf* (1883, p. 47):

Eine Systematik im Sinne der anderen Pflanzengruppen ist für die Spaltpilze zur Zeit insofern nicht möglich, als es an einer entwicklungsgeschichtlichen Durcharbeitung des Gebietes noch gänzlich fehlt.

The curious change in *Brefeld's* view, which led him (1908) to the assumption that it is a priori erroneous to undertake any investigations upon the life history of the bacteria, though he, too, had advocated such studies at an earlier date (1881), is a good example of the blighting effect exerted by the rigid monomorphistic dogmatism propagated by the orthodox followers of *R. Koch*.

Even *F. Cohn* has once (1872*b*, p. 130) emphasized the necessity of thorough investigations upon the life cycles of the bacteria (see quotation on p. 11), though he abandoned later this standpoint more and more. But it is still more surprising that an author like *Fraenkel* (1891), who did not hesitate to declare any type of growth or any reproductive organ which was not approved by *R. Koch* as an entirely superfluous, "illegitimate," degenerate by-product (see quotation and critique on p. 27), nevertheless admitted that no definite arrangement of the system of the bacteria could be made, because:

Der nötigen entwicklungsgeschichtlichen Durcharbeitung entbehrt das ganze Gebiet noch zu sehr, als dass ein solches Vorgehen schon am Platze wäre (p. 13).

The more correct opinion, which during the last two decades has gained some ground among German and Austrian bacteriologists, has naturally evoked new interest in such studies. It was especially the Austrian authors *W. Winkler* (1899), *Mencl* (1905), and *Fuhrmann* (1906–1913) who recommended a renewed close study of the complete life cycles of the bacteria and themselves contributed some important findings from this field.

Although the full discussion of the data secured by such investigations upon the life history of certain species will better find its place on the following pages, a short compilation of the names of the authors and of the organisms, studied by them, may be inserted here. It is of great interest for three reasons: First, practically all these studies have been made quite independently and the good agreement of the results obtained is, therefore, of increased importance. In the second place, it is of great value that representatives of all groups of bacteria have been tested and analogous results have been recorded with all of them. In the third place, it becomes evident that the necessity of such studies has been felt quite generally; among the authors who have done such work practically all nationalities are represented.

The careful studies of *Thiercelin* (1899–1903) on the various developmental stages of his Enterococcus will prove helpful for further investigations upon the streptococci. *W. Winkler* (1899) obtained very important data with *B. coli*, *fluorescens*, *aquatilis*, and with a yellow, nonspore-forming rod (probably *Bact. herbicola*), which he rather incorrectly named *B. mesen-*

tericus aureus. *Hauser's* early work upon his Proteus (1885) furnishes a practically complete picture of the life history of this group of organisms. *Fuhrmann* (1906–1908) studied the life cycles of his *Pseudomonas cerevisiae*, several Fluorescentes, and of some other rods. *Almquists* investigations (1893–1917) were especially concentrated on the typhoid bacillus and the cholera vibrio. The latter had also been the object of the little known work of *Ferrán* (1885) and of *Dowdeswell* (1889–1890). *Finkler* and *Prior* (1885) gave a fairly complete report upon the life cycle of their vibrio, isolated from Cholera nostras. *Albrecht* and *Ghon* (1900), *N. K. Schultz* (1901), as well as *Rowland* (1914), have furnished valuable contributions to the complete knowledge of the life history of *B. pestis*. *Rosenbach* (1909) did the same concerning the bacteria causing erysipeloid, rouget and septicaemia of mice. The life history of some organisms closely related to Friedländer's Pneumonie bacillus was described by *Bordoni-Uffreduzzi* (1888) and by *Jehle* (1902). *Johan Olsen* (1897) investigated the life cycle of *B. mycoides* and of other spore-forming bacilli. The glanders organism has been studied along similar lines by *Carpano* (1913), the leprosy organism by *Lutz* (1886), *Barranikow* (1900), and by *Kedrowski* (1901), the tubercle bacillus by *Schroen* (1886–1904) and by *Maher* (1910–1913) and the Corynebacteria by *E. de Negri* (1916), and by *Bergstrand* (1918). *Krzysztalowicz* and *Siedlecki* (1908), as well as *McDonagh* (1912–1913) made the life history of *Spirochaeta pallida* the object of their investigations. In *Meirowsky's* "Studien über die Fortpflanzung von Bakterien, Spirillen und Spirochaeten" (1914 *b*) for the first time representatives of very different groups (*B. tuberculosis, leprae, paratyphi, enteritidis*, various spirilla, and spirochaets) have been made the object of a thorough comparative research. Of equal or even greater importance are the investigations of *Hort* and his collaborators (1915–1917), who worked with meningococci, typhoid, paratyphoid, dysentery, and colon bacilli. And in our own experiments upon the life cycles of the bacteria (1916) representatives of practically all groups of bacteria, except mycobacteria and spirochaets, have been included.

Fig. 1 on Plate A taken from our first paper (*Löhnis* and *Smith*, 1916 *a*) shows in a schematic arrangement the rather complicated life cycle of *B. azotobacter*, and a glance at the two Tables II A and II B, taken from the same paper (pp. 683 and 689) and revised with regard to some additional findings mentioned in our second preliminary communication (1916 *b*), reveals at once the important fact that essentially the same types of growth occur in the life cycles of all different kinds of bacteria.

TABLE II A.—*Types of growth observed with 24 cultures of Azotobacter.*

[The laboratory numbers of the cultures are given at the head of the columns.]

Types of growth. (For explanation of letters see Table II B.)	Azotobacter Chroococcum stock cultures.		Azotobacter Beijerinckii.				Azotobacter vinelandii.	Azotobacter vitreum.	Azotobacter chroococcum stock cultures.			Azotobacter Beijerinckii.	Azotobacter chroococcum.	Azotobacter Beijerinckii.	Azotobacter vinelandii.	Azotobacter chroococcum stock cultures.				Azotobacter chroococcum new isolations.				
	1	2	3	4	5	6	7	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C	+	+	+	+	+	....	+	+	+	+	+	+	+	....	....	....	+	....	....	+	+	+	+	+
D	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
E	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
F	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
G	....	+	....	+	....	+	+	....	+	+	+	+	+	+	....	+	+	+	....	....	+	....	....	+
H	+	....	....	....	....	....	+	+	....	....	+	....	+	....	....	+	+	....	....	+	+	+	+	+
I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
J	....	....	....	....	....	....	....	....	....	+	+	....	+	....	....	....	+	....	....	....	+	+	+	....
K	+	+	+	....	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
L	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
M	....	....	+	....	....	....	....	....	....	+	+	....	+	....	....	....	+	....	....	....	+	+	....	....

TABLE II B.—*Types of growth observed with 18 representative bacteria.*

[The laboratory numbers of the cultures are given at the head of the columns.]

Types of growth.	B. subtilis.	B. lactis niger.	Tyrothrix tenuis.	B. danicus.	Bact. pneumoniae.	Bact. radiobacter.	Bact. denitrificans agile.	Bact. radicicola.	Bact. fluorescens.	Yellow bacillus.	Planosarcina ureae.	Sarcina flava.	Midr. candicans (soil).	M. (candicans milk).	Salt Lake spirillum.	Ocean spirillum.	Streptoc. lactis.	Bac. bulgaricus.
	31	32	33	34	35	36	38	39	40	41	42	43	44	45	46	47	48	49
A (large globules and ovals)	+	....	....	+	+	....	....	....	+	+	+	+	+	+	....	....	+	....
B (thick walled forms of type A)	+	+	+	+	+	....	....	....	+	+	+	+	....	....	....	....	....	+
C (granular decomposition of A, B, L, M)	+	+	+	+	....	....	....	....	....	+	+	+	+	....	....	....	....	+
D (symplasm)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
E (small globules and ovals)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
F (small rods and threads)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
G (slime threads with cocci)	....	+	+	+	+	+	+	+	+	+	+	+	....	....	....	+	....	+
H (granular decomposition of F and of spores)	+	+	+	+	+	+	+	+	+	+	+	....	+	....	....	....	....	+
I (regenerative bodies)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
J (normal cells developing inside)	+	....	+	+	....	....	....	....	....	+	....	....	....	....	....	....	....	....
K (budding gonidia)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
L (large rods and threads)	+	+	+	+	+	....	....	+	+	+	+	....	+	+	....	....	+	+
M (cells with pointed ends)	....	+	....	+	....	+	+	+	+	....	....	+	+	+	....	....	+	+
N (starlike growth)	+	+	....	....	+	+	+	+	+	+	....	....	+	+	+	....	+	+

The detailed discussion reserved for the following pages will bring additional proof that a fairly correct insight into the little-known life history of the bacteria is obtainable at the present time, provided that those observations are carefully considered which practically always have been laid aside because they were incompatible with the prevalent doctrine, and in their isolation they had not sufficient weight to command attention and to instigate renewed experimental investigations.

It is beyond doubt that such investigations will lead to an incomparably better knowledge of the real morphology and physiology of the bacteria. The present situation in bacteriology is very much like that confronted by *Tulasne* (1851) in mycology, in regard to whose work *De Bary* (1884, p. 129) said:

Anknüpfend an wenige und immer wieder zurückgedrängte Beobachtungen unternahm er zu zeigen, dass die Formspecies der bisherigen Mycologie in vielen Fällen nicht für sich allein Speciesrepräsentanten sind, sondern dass eine solche Formspecies mit anderen dem Entwicklungskreise einer wirklichen Species angehören kann.

What has been written by *Sachs* (1875, p. 214) about the algae holds equally true to-day concerning the bacteria:

The discovery of alternation of generations and polymorphism in some sections justifies the supposition that certain forms not as yet accurately known may be merely conditions of development of unknown cycles of forms, although hitherto considered distinct species and genera.

That a complete knowledge of bacterial ontogeny is absolutely necessary for securing a well-founded insight into the phylogeny of these organisms is beyond question, since *Haeckel* (1876) has shown how the development of the tribe is reproduced in the life history of its members. *Hueppe* (1886, p. 41, 149), *Kruse* (1896*c*, p. 492), and *Fuhrmann* (1906) have already emphasized the importance of this fact in regard to bacteriology.

(c) THE STUDY OF PLEOMORPHISTIC PROBLEMS.

It goes without saying that in every case where morphological and physiological alterations of the bacteria are made the object of more or less thorough studies all five explanations discussed on the foregoing pages will have to be taken under consideration. Thus far dogmatism and standardization have acted too frequently as some kind of "theoretical blinders" in bacteriological investigations. Moreover, the practical aims of most of the work done, and the resulting impossibility to follow up interesting new observations in a correct scientific manner, have also to be borne in mind as important reasons why the whole situation is still so unsatisfactory. To discard indiscriminately all unexpected cases as "contaminations" and "involution forms" is a practice which certainly should not be followed more frequently than is absolutely necessary.

To decide correctly which explanation will be applicable in one or the other case is not always easy. It may be done either by continuous, direct, microscopical examination or by isolating and studying single-cell cultures, or by comparing results of suitably arranged and sufficiently extended parallel experiments. Every one of these three ways has its advantages and disadvantages; none of them is principally superior to the others.

The continuous direct microscopic examination has been repeatedly declared to be the only manner in which convincing results can be secured. However, this categorical statement is more the outgrowth of unscientific dogmatism than the result of experimental experience. In some special cases direct continuous observation is, indeed, highly recommendable, or even indispensable. Formation and germination of spores and of other reproductive organs, budding and branching, the occurrence and meaning of apparently sexual processes, for instance, are some points which will be studied advantageously with the living material under the microscope. In other cases other ways will be preferable for securing conclusive results. What *De Bary* (1884, p. 137) said is, of course, indisputable:

Das erste Postulat einer morphologisch-entwicklungsgeschichtlichen Untersuchung ist der Nachweis der organischen Continuität successiver Entwicklungszustände.

But it is very disputable whether the highly unnatural conditions prevailing in a hanging drop or agar block preparation on the stage of a microscope are best suited to bring out the normal developmental stages characteristic for the bacterial life under natural conditions.[1]

It should also not be overlooked that many of the older publications upon the pleomorphism of the bacteria have been the result of patient continuous microscopic studies. And yet practically all of them have been discarded as not convincing, some of them certainly with good reason. The latter holds true, e. g., for many of *Hallier's* discoveries. But even the reports of such well-trained investigators like *Rindfleisch* (1872), *Klebs* (1875 *a* and *b*), and *Cienkowski* (1877), who unanimously stated that they directly observed the change of coccus to rod-forms and vice versa, were later not accepted as conclusive proof against the monomorphistic dogma: that a coccus is always a coccus and a bacillus a bacillus, "and any evidence which may be presented to the contrary is based upon untrustworthy methods of observation" (*A. C. Abbott*, 1902, p. 51). *Zopf's* fundamental researches upon the pleomorphism of the bacteria (1881) were all based on direct continuous observation, and that *Winogradsky's* opposite findings, (1887–1888), which by monomorphistic writers have always been quoted as final evidence against *Zopf's* work, though they were obtained with the same method and with impure cultures, too, that they, in fact, are by no means very accurate and convincing, has been sufficiently shown by *Zopf* (1895) in a special reply, which hardly ever has been quoted. That it is possible to keep a form constant for some time under constant conditions, as *Winogradsky* has shown in these experiments, is beyond question. Millions of cultural experiments made according to standardized methods have confirmed this fact. But it is equally beyond question that such highly artificial experiments, in which no attention is paid to the innumerable modifying influences of time and environment, constantly present and active in nature, can at best be accepted only as part of the truth. As early as in 1880 *Neelsen* emphasized quite correctly, after having discussed the various difficulties which may reduce the value of experiments based on direct observations, especially in the case of motile organisms:

Endlich aber wäre selbst nach glücklicher Überwindung aller dieser Schwierigkeiten noch nicht viel gewonnen; man würde zwar ein Bild des Entwicklungsganges haben, wie er in einem bestimmten, sich gleich bleibenden Medium abläuft, aber dadurch keine Kenntnisse erlangen von den Modificationen dieses Cyclus, respective den anderen Formen des Wachstums und der Fortpflanzung, wie sie in Medien von anderer und wechselnder Zusammensetzung vorkommen.

Gruber (1885) and others have published similar critiques. *Metchnikoff* (1889 *b*) wrote against *Winogradsky* that the continuous observation in the living state can not be considered to be a "conditio sine qua non":

Il ne faut pas oublier qu'il existe un grand nombre de parasites dont l'évolution ne peut presque pas être étudiée sur le vivant et dont le developpement est néanmoins suffisement connu.

[1] In 1874 *Billroth* wrote in this respect: "Man würde auf diesem künstlichen Wege nur die unvollkommensten, dürftigsten Formen erzeilen, welche von den ausgebildeten so verschieden sind wie Hafer im Zimmer auf feuchte Watte ausgesäet von üppigem Hafer auf gutem, cultivierten Feldboden."

More recently *Meirowsky* (1914 *b*, p. 84) has pointed out that especially in the case of the protozoa nobody has been able to follow the whole life cycle of any species by continuous direct microscopic observation:

Auch hier hat kein Auge an einem Exemplar den Zyklus ablaufen sehen, sondern man hat auf die Entwicklung aus verschiedenen, auf einander folgenden Bildern geschlossen.

The use of single-cell cultures has also been strongly recommended more recently, especially for solving problems in bacterial variability. A paper by *Cole* and *Wright* (1916) upon the application of the pure-line concept to bacteria is a characteristic example how easy it is to put forth such purely theoretical demands without furnishing any experimental support. They believe that "pure lines" would show great constancy, but it is not mentioned in their paper that actually all experiments which have been made so far have shown without any exception that single-cell cultures give exactly the same results in pleomorphism and variability as do pure cultures obtained from plates. The investigations of *Kowalenko* (1910), *Baerthlein* (1911), *Bernhardt* (1912), *Nyberg* (1912), *Penfold* (1912), *Fürst* (1914), *Rosenow* (1914), and of *Almquist* (1917) have brought out this fact sufficiently. *Baerthlein*, *Bernhardt*, *Nyberg*, *Penfold*, and *Almquist* confirmed their own experiments, but it is of special interest that *Fürst* was able to confirm with his single-cell cultures of the *Finkler-Prior* vibrio the results obtained by *Firtsch* (1888) about 25 years earlier. The same holds true concerning *Rosenow's* new experiments upon the streptococci, as a counterpart to those of *Kruse* and *Pansini* (1892), and in regard to *Kowalenko's* Coli studies, as compared with those of *M. Neisser* (1906) and *Massini* (1907).

That by no means every colony appearing on the plate represents the pure progeny of a single cell is an indisputable fact. But it is equally certain that repeated plating, controlled by careful microscopic studies, and eventually supplemented by passage cultures in other substrates, will finally furnish exactly the same "pure lines" as any of the single-cell methods. It is difficult to understand why a method, which always has been accepted as quite reliable as long as the results obtained with it have been in accordance with the monomorphistic theory, suddenly should become so highly suspicious, as soon as some conflict arises between preconceived ideas and the facts before our eyes.

It is not to be denied that the study of single-cell cultures will occasionally prove very helpful, or even necessary. All methods thus far devised for this purpose, however, have their conspicuous disadvantages. The frequently very unsatisfactory growth of the isolated cells is one of them. In *Barber's* (1907) experiments, e. g., 40–70 per cent of *B. coli*, otherwise so readily propagating on all substrates, failed to grow. *Fürst* (1914) succeeded with *V. proteus* in only 10 per cent of all cases. That the chances for contamination are considerably increased should also never be forgotten.

Generally, therefore, the standard methods which otherwise have proven their reliability during the last decades will also have to be considered in the first place for conducting experiments upon the life history of the bacteria. If we only abstain from the unscientific practice to discard, without adequate testing, every culture showing some unexpected development as "contaminated" or as containing "merely involution forms," and every slide as "not sufficiently clear" which shows something more than the monomorphistically trained eye is inclined to see, those methods will usually prove quite satisfactory, provided that a sufficient number of parallel experiments is suitably arranged, long enough continued and several times repeated.

This latter point has been strongly emphasized by *Gruber* as early as in 1885, when he first attacked the monomorphistic dogma then proclaimed by *R. Koch's* followers (with "religious fanaticism" as *Gruber* says). His own experiments showed him that globular, rod-like and spiral forms are merely types of growth, not distinctive marks of species and of genera. Changes from one form into the other were observed with pure cultures as often as the experiments were repeated, and it was always possible to retrace the intermediate steps to the starting point. In his "mutation" studies *Baerthlein* (1911) also accepted the uniformity of the results obtained in a great number of parallel experiments as full proof of their validity. *Nyberg* (1912) equally pointed out that it would be entirely improbable to

assume, that accidental contaminations would cause the uniform results which he secured with 140 strains of various lophotrichous rods, all producing the same types of pleomorphous colonies. *Bernhardt* (1915, p. 219) made the following remark upon this subject:

Wer zahlreiche derartige Umwandlungsversuche an verschiedenen Bakterien Monate hindurch selbst verfolgt und sich immer wieder von neuem davon überzeugt hat, dass bei jeder Bakterienart die Veränderungen doch immer nur in ganz bestimmter Richtung erfolgen, wird kaum je Schwierigkeiten haben, die Verunreinigungen, die selbstverständlich auf alten Platten nicht ausbleiben, als solche zu erkennen.

That experiments of short duration are hardly of any value has been discussed before (see the quotations from *Adami* on p. 33, and from *Stamm* on p. 34). The very great persistency exhibited by some strains, as observed, e. g., by *Stamm*, may occasionally test the patience of the investigator very much. However, appropriate experimenting usually will eliminate difficulties arising from this source.

It has also been mentioned before that not infrequently strict adherence to monotonous standardized laboratory methods has hindered, and will perhaps further delay such progress as should and could have been made in bacteriology long ago. There is unquestionably a very wide gap between the highly artificial conditions under which the pure cultures are often compelled to live in the laboratory and the actual situation the bacteria are confronted with in nature. In this respect it should be borne in mind that various strains of the same species of bacteria when recently taken from their natural habitat not only differ more or less from strains of the same species kept for some time in "solitary confinement" in the laboratory, but they also show very often considerable incongruencies when compared with each other. Sets of accumulation experiments, as recommended by *Beijerinck* and others, demonstrate this fact conclusively. The interesting results obtained by *H. M. Ward* (1895 *a*) and by *Stamm* (1914) in their studies upon the development of bacteria in water, also show clearly the sometimes deeply alterating influences of a more natural surrounding. In our first preliminary paper upon the life cycles of the bacteria (1916 *a*, p. 685) it was pointed out that it was very easy to obtain full insight into the complete life cycle of *B. azotobacter* by inoculating all the strains on hand (numbering 22) into their natural substrate, viz., into soil. The important results obtained by *Almquist* in regard to the life cycles of pathogenic bacteria are also mostly due to a studious application of the conditions to which these organisms have to adapt themselves when living naturally as saprophytes.

A comparison of the different influence of the natural and of the more or less artificial conditions as given in the laboratory would be rather incomplete, however, if the effect caused by symbiotic interaction would not find due consideration. That physiological activities can be, and often are, deeply altered, when bacteria are growing in symbiosis has been repeatedly noticed. Details are to be found in the publications of *Cornil* and *Babes* (1890, Vol. I, pp. 229–237), *Th. Smith* (1894), *Kruse* (1910, p. 168), and others. But so far comparatively few observations have been recorded which indicate that in morphological studies equally unexpected results may be caused by symbiosis. *Lorenz* (1892) obtained a clearly actinomyces-like growth of *B. erysipelatos suum*, when he inoculated this organism in a filtered culture broth of *B. suisepticus*. In gelatin, as well as in the animal, the bacilli reverted promptly to their "typical" appearance. But more recently *Rosenbach* (1909) has demonstrated that the complete life cycle of the organism named, as well as of those closely related to it (erysipeloid and septicemia of mice), embraces, indeed, such an actinomycotic phase. *Metchnikoff* (1894) found large club and dumb-bell-shaped forms with lateral buds in a cholera culture, which contained a white coccus. From other researches, especially from those of *Dowdeswell* and of *Stamm*, it is known that these forms, too, belong to the normal life history of *V. cholerae*. *Metchnikoff* points out:

La constance de cette modification indique une influence particulière du coccus blanc sur les fonctions du vibrion.

Kurth (1898) discovered that the diphtheria bacillus is much inclined to change its appearance whenever other organisms are present. Symbiosis with *Streptococcus lanceolatus* caused the development of very short forms, which were hardly discernible from the pneumococci

themselves. Ten years later *Smirnow* (1908) made exactly the same observation, from which the following conclusion was drawn:

> The change in morphology of the Klebs-Loeffler bacillus to a coccus and the return to its bacillary form is interesting, as it indicates the possibility that bacteria may change their morphology under certain favorable or unfavorable conditions.

Similar changes were also observed in these experiments when the two organisms were cultivated in "double test tubes" (one within the other), so that only the metabolic products could penetrate into the other culture and no streptococci could be mistaken for diphtheria bacilli, and vice versa. As practically all cases of diphtheria present mixed cultures of *B. diphtheriae, streptococci,* and other symbionts, the importance of these findings is evident, especially when combined with the fact that several entirely independent observations have been recorded, where nothing but coccoid forms were found in cases of true diphtheria (*Dale,* 1910; *Balfour,* 1911 *d*). Some observations of *Heinemann* (1917), on the other hand, clearly indicate that also in this case the "illegitimate" forms are, in fact, part of the normal life cycle of this species, and analogous findings have been made with diphtheroid organisms by *Walker* and *Adkinson* (1917), as well as by *Mellon* (1917).

The olive-tubercle organism studied by *Petri* (1907) quickly assumed characteristic "involution" forms when grown together with *Ascobacterium luteum.* The changed forms remained also in this case capable of further propagation.

Babes (1893) secured development of the fusiform bacilli found in cases of scurvey, as well as in the normal mouth, only in such agar where streptococci had been grown before, and here the bacilli also produced curved threads "longer and thinner than cholera bacteria." *Proca* (1908) found anew that *B. fusiformis* grows much better in symbiosis with *B. subtilis* or *streptococci* than alone. The typical spirochaete-like spiral forms with pointed ends found by other investigators in pure cultures of *B. fusiformis* appeared readily in broth cultures of the symbionts.

The highly interesting diphtheria-like forms (club-, dumb-bell-, spindle-shaped, etc.) first seen by *Babes* (1895) in pure cultures of the streptococci were also produced much more abundantly by the so-called *Bact. Guentheri* (*Streptococcus lactis*) when grown in symbiosis with *B. putrificus* (*A. Wolff,* 1908). *Lorenz* (1909) noticed that the very pleomorphous streptococcus, isolated by him from horses afflicted with "Brustseuche," gave a distinctly Streptothrix-like development when cultivated together with an Aspergillus. *Rosenow* (1914), too, emphasizes the importance of symbiotic effects in his report on the transmutations within the Streptococcus-Pneumococcus group.

That occasionally such experiments with mixed cultures may be of great advantage in solving special problems in regard to the life history of one or the other organism may be seen from the following experience. One of my two Azotobacter strains, which first had passed over into thin spore-forming rods, reverted readily back to the characteristic large round Azotobacter type when cultivated under suitable conditions (in mannite soil extract). The other, however, remained absolutely stable despite repeated transfers. Considering the fact that in nature Azotobacter always is to be found in symbiosis with *B. radiobacter,* this organism was added with the result that in very short time the large form reappeared, though it turned out to be very unstable after renewed isolation (*Löhnis* and *Hanzawa,* 1914, culture No. 6, figs. 15–19). In another experiment made by *Kuntze* (1904) a similar case has been observed. *B. oxalaticus,* whose pure cultures when kept for some time on artificial substrates quickly assumed the "normal" Subtilis-like appearance, looked very much like Azotobacter when growing in symbiosis with the so-called *B. denitrificans agilis,* which is probably a denitrifying variety of *B. radiobacter.* Moreover, as early as in 1884 *DeBary* (p. 503) reported that his *B. Megaterium* grew in rows of large cocci, which also broke up into single cells, and which never produced spores (all this like Azotobacter) when this organism was kept in mixed culture with a small bacterium whose identity has not been established, but that they reverted to the typical spore-forming bacilli when separated from this symbiont.

The remarkable uniformity of the results obtained in these three cases may be accepted as another indication that it seems to be recommendable for a correct study of the complete life

history of the bacteria to take under due consideration also such biological influences, permanently active in nature, in addition to the many physical and chemical factors which may often cause important reactions on the side of the bacteria. These, perhaps, never would be discovered if we continue to adhere too closely to the ordinary laboratory methods.

It is beyond question that our knowledge of the true life history of the bacteria is still very inadequate, and that we are far from knowing all facts about them which we should know. That the ascertainment of these data is absolutely necessary before any correct decision can be reached concerning the true character and the systematic position of the various species of the bacteria has been emphasized by numerous authors, like *Klebs* (1875*b*), *Davaine* (1876, p. 20), *Gruber* (1885), *Hueppe* (1886, p. 84; 1891, p. 27), *Cornil* and *Babes* (1890, Vol. I, p. 18), *R. Koch* (1890), *Beijerinck* (1898), *H. M. Ward* (1910), and others. With regard to *Zopf's* classification, which at least tried to make use of what was known at that time upon the life history of the bacteria, *H. M. Ward* made the following remarks in his important paper "On the Characters, or Marks, Employed for Classifying the Schizomycetes" (1892), which also at the present time deserves our attention:

> *Zopf's* classification, admirable as it is in many respects, is difficult to work in practice, because it is necessary to have all the stages of development before we can decide on the position of a species; at the same time it should be noted that in this very respect it is far ahead of the merely tabular classifications, used for hurriedly determining the name of a form, as a good flora is ahead of a mere museum catalogue of plants . . . It is, in fact, just in respect of this particular attention to all the facts in the development of the species that *Zopf's* classification is scientifically so far in advance of his predecessors . . . The matter of difficulty of application can not be urged as a reason for desisting from obtaining and recording all that can be discovered regarding an organism . . . On the other hand, pathologists, hygienists, chemists, etc., often do not care, what vagaries the organism exhibits, so long as they can recognize it when they meet with it. As a matter of experience, however, it is just these vagaries that bring about the sources of error which beset them on all hands, and hence they are equally interested with the botanist in having them cleared up, and explained.

It has been pointed out before, that it is a fundamental mistake to assume that the acknowledgement of the pleomorphous character of the bacteria be equivalent to an attempt to obliterate all bacteria species. That many of the so-called species, introduced into the literature, often by the dozens, by quite inexperienced recruits in bacteriology, will have to disappear is of course, beyond question. Such an elimination of entirely worthless ballast, however, has, nothing at all to do with a cancellation of well described species. The narrow limiting of species, as advocated by *F. Cohn, R. Koch, Winogradsky, Migula* and others, should have been abandoned long ago, and, as was shown by numerous quotations, it has indeed already met with much well justified opposition. *Jordan* (1909, p. 339) aptly remarks:

> The features that should characterize a bacterial race or species have not yet been established, and until some consensus of opinion on this point has been reached, discussion of specific identity is futile."

The following lines by *E. F. Smith* (1905, p. 155) are equally worth quoting in this connection:

> Many names have been given unaccompanied by any proper description of the organism . . . To found, for example, a new species of rabbit on the observation that a small jumping animal about the size and shape of a rabbit has congregated in certain turnip fields and caused great damage, and apparently had destroyed no other plants, would only serve to provoke a smile or to raise a doubt as to the author's mental condition, and yet descriptions equally worthless are not at all uncommon in systematic bacteriology.

A still earlier statement made by *Hill* (1902*a*) has also lost nothing of its validity:

> It is easy to say that the whole subject needs much development before consideration of the names to be employed is necessary. Names, indeed, can not be intelligently selected until the facts themselves are thoroughly established and correlated.

So far, the variability of the bacteria alone has been more closely considered in connection with these problems, and it was usually from this point of view that the establishment of well-defined groups has been advocated by European and American authors. That truly natural species can be founded, however, only after a much more thorough knowledge of their complete life history will be available, hardly needs to be emphasized. The details discussed on the following pages will help to make clear how much work remains to be done along these lines, and what new insight into the natural relationship among the bacteria may be gained from

such studies. Moreover, these facts in their entirety furnish a welcome support to the following statement made in our first preliminary report on this subject (1916*a*, p. 677):

The development of the bacteria is characterized not by the irregular occurrence of more or less abnormal forms, but by the regular occurrence of many different forms and stages of growth, connected with each other by constant relations.

Unquestionably many so-called species, frequently described in the most superficial manner, will have to be cancelled, because they merely represent fragments of the life cycles of other bacteria. Good species, on the other hand, will not only keep their position, but they will receive a much more complete and sharper definition than they now have.

2. MORPHOLOGY OF THE DIFFERENT GROUPS OF BACTERIA.

(a) COCCI.

That the old form-genera Micrococcus, Sarcina, and Streptococcus each comprise severa groups of organisms which will present themselves as natural genera as soon as their full life cycles will have been studied is already clearly indicated by several observations recorded thus far. That, however, such highly variable marks as pathogenicity and pigment production can not be considered to be of fundamental value in this respect has been discussed. (Concerning pigmentation of micrococci see especially *Neumann*, 1897; in regard to pathogenicity of micrococci, *Geisse*, 1914; of streptoccoci, *Heinemann*, 1915, and upon carbohydrate fermentation of streptococci, *Broadhurst*, 1915, and *Henrici*, 1916.) It is quite true that Micrococci as well as Streptococci exhibit a rather well recognizable general character. But there is a number of cases where it is difficult or even impossible to decide clearly whether the organism should be classed as a Micrococcus or as a Streptococcus. When I (1907) tried to arrange the numerous so-called species of lactic acid bacteria and their relatives in some fairly well defined groups, I had to dwell upon this particular point. Soon afterwards *Babes* (1908) showed experimentally that even an otherwise typical *Staphylococcus aureus* may occasionally assume the morphological appearance of a Streptococcus. To the same author we owe the first distinct results concerning the close relationship existing between Streptococci and the diphtheria group (*Babes*, 1895). The analogous relations connecting micrococci and actinomycetes have been more recently emphasized by *Beijerinck* (1914*a*). Comparatively the most conspicuous heterogenicity is noticeable among the Sarcinae. Some of them are undoubtedly merely types of growth of micrococci. (See *Lehmann* and *Neumann*, 1912, p. 198; *Löhnis*, 1907, p. 146.) Others, however, evidently belong in the life cycle of typical rods, especially of spore-forming bacilli.

That most of the so-called Micrococcus species created by *F. Cohn* were no micrococci at all has been mentioned on page 11. And it has also been pointed out that statements made by *Fraenkel* and *Pfeiffer* (1895), *A. C. Abbott* (1902), and others, maintaining that an absolute constancy of the cell form is to be found with the micrococci, are in open conflict with numerous well established facts.[1])

It may happen, of course, that one or the other strain will be temporarily constant, sometimes even for a comparatively very long time. In our experiments, e. g., two strains of *Micrococcus candicans*, one from Russian soil, the other from evaporated milk, exhibited very readily and in a quite uniform manner the characteristic stages of their life cycle, of which some forms are reproduced in figs. 1–4, Pl. I, while on the other hand a *Micrococcus luteus* was quite irresponsive; but a careful search revealed in this case, also, at least some inclination to form the large club forms characteristic for this group. The use of salted substrates has helped *Matzuschita* (1900) to get the peculiar rod-like forms with *Micrococcus rubefaciens* and *M. flavus*, as shown in figs. 5 and 6 on Pl. I [2], while *Maassen* (1904) and *Péju* and *Rajat* (1906*e*) did not see any alteration of the micrococci tested on similar substrates. The yellow *Kokkobacillus*

[1] In the explanation to Table I of their "Atlas," *Fraenkel* and *Pfeiffer* say: "Mit grosser Zähigkeit halten die Mikrokokken unter allen Umständen an der ihnen eigentümlichen Form fest, und mit Recht werden sie deshalb auch als der beste Beweis für das vielumstrittene Gesetz von der Constanz der Form bei den Bakterien angesehen. Äussere Einflüsse jeder Art bleiben dieser Eigenschaft gegenüber vollkommen machtlos, und ein echter Mikrokokkus erscheint stets nur in seiner streng kugligen Gestalt."

[2] In these two cases the rod-like forms were abundant, whereas with *M. luteus, candicans, aurantiacus, coronatus, flavus desidens, aërogenes Sarcina lutea*, and *agilis* only occasionally stretched forms became visible among the cocci.

zymogenes, isolated by *Biedert* (1885) from saliva, grew as a coccus, rod, or thread. Some of the straight forms contained coccoid bodies, whose further development was not observed. The yellowish "Mikrokokkus B" of *Malapert-Neufville* (1886, p. 57) from water showed at first typical globular forms, but stretched later into distinct rods which in their turn broke again into micrococci. The yellow *Micrococcus subnormalis* of *Hopkins* (1898) from the human mouth grew at first on agar, gelatin, broth, and potato as a rod, later as a coccus; on serum, however, it showed the form of a coccus from the start. Whether these three organisms were identical or not must naturally remain an open question, though it seems quite possible. The photographs accompanying *Hopkins'* paper are very much like our pictures of *M. candicans*. Even branching and budding are clearly visible, although they were not mentioned by the author. Changes from cocci to rods, diphtheroid and yeast-like forms also have been recorded by *Young* (1914).

Best known, however, are the transformations exhibited by *M. melitensis*, which species, on account of its morphological instability, has been transferred more recently by some authors to the bacilli. *Durham* (1898), who published the first fairly correct description of this organism, found out that both agar and broth gave exclusively micrococci when kept at 37° C, while at 18–20° after a few weeks almost exclusively bacilli were visible, about two to four times longer than broad, and sometimes curved. But brought back to 37° they reverted to "the ordinary coccus form in pure culture." *Babes* (1903) gave another description and good pictures of *Micrococcus melitensis*. Part of the forms, especially those of club-like appearance, resemble very much certain pseudo-diphtheria bacilli. According to *Babes'* opinion, relations may exist with bacteria occurring in bronchitis and whooping cough, perhaps also with the influenza bacillus. *Günther* (1906, p. 771), as well as *Lehman* and *Neumann* (1912, p. 231), consider the organism to be a coccus which occasionally produces rod-like, clubbed, and other forms. *Jordan* (1916, p. 416) calls it *Bac. melitensis*. The picture accompanying his description, reproduced as figure 7 on plate I, makes an interesting counterpart to the rod-like forms of other cocci (figs. 2–6); in the center of figure 7 cocci are seen to bud out of a rod-form, and very similar things are visible in figure 8. The rods exhibit in all these cases the same irregular appearance, as is common with the Mycobacteria (especially with those of the diphtheria group). *Eyre* (1907) is strongly opposed to the idea of placing *M. melitensis* among the bacilli. He thinks that all bacillary forms are either stretched cocci or irregular "involution" forms. His figure 2 shows all types pictured in our photographs of *M. candicans*. Exactly opposite is *Saisawa's* (1911) standpoint. This author is certain that the organism is a typical short rod, not a coccus. In his photographs cocci budding forth from rods are again very conspicuous, but in the paper itself nothing is said about this interesting fact. *Evans* (1918) made the interesting discovery that six strains of *M. melitensis* behaved morphologically and biochemically, as well as in the agglutination test, as did *B. abortus*.

The organism introduced by *F. Cohn* (1872) as *Micrococcus phosphoreus* is at present classified, probably by all authors, as *Bacterium phosphoreum*. According to *Molisch* (1903, 1904, p. 60) typical cocci are exclusively formed on salted agar, while in salted gelatin all kinds of irregular rods, clubs, etc., become visible. On agar and potato cocci were found in the beginning, which were later supplanted by rods, clubs, and branched forms.

F. Cohn's Micrococcus cyaneus has been studied anew by *Beijerinck* (1914 *a*) and renamed *Actinococcus cyaneus* on account of its relationship to Actinomyces. It grows usually blue, but red in acid-producing varieties, and white when reinoculated from old material. According to the Dutch author the new genus Actinococcus should embrace all micrococci which exhibit clearly Actinomyces-like characters, and it should be placed in the neighborhood of Corynebacterium, Mycobacterium, and Actinomyces.

In this connection, and in addition to the confirmative results mentioned above, the old observations of *Rabe* (1886) concerning his *Micrococcus botryogenus* regain new interest. Growth within the body looked very much like the well-known clusters of Actinomyces. (See fig. 276 on Pl. XXII.) On the artificial substrate, however, only normal micrococci grew, though in the clusters short chains were seen, as were also obtained in cultures by *Babes* (1908).

Several other little known species, viz., *M. coronatus Flügge*, *M. coralloides Zimmermann*, *M. viticulosus Katz*, *M. polypus Mig.*, *M. nubilus Fontin*, and *M. vesicae Heim* (see *Lehmann* and *Neumann*, 1912, p. 234–235) are interesting on account of their tendency to form branches around the edge of their colonies and along their stab cultures in gelatin. The inclination to assume rod-like forms seems also to be not uncommon in these cases. *M. viticulosus* reminded *Lehmann* and *Neumann* (1912) somewhat of their *Bacterium vulgare* (Hauser's Proteus).

Meningococci and gonococci are also by no means the simple constant cocci, which they are often supposed to be. The meningococci are especially inclined to exhibit a great variability in their cell form, as well as in their stainability. The occurrence of very small up to very large cells has been declared by *Kutscher* (1907) to be characteristic for this species. Small cocci were seen by *Lehmann* and *Neumann* (1912, p. 223) attached like buds to the large, deeply staining "giant" forms. That the positive or negative reaction with the Gram method can not be used to distinguish two different species (the *Diplococcus intracellularis meningitidis Weichselbaum* and the *Meningococcus intracellularis Jaeger*) is proven by the investigations of *Köhlisch* (1915) and of *Hort*, *Lakin* and *Benians* (1915). According to *Köhlisch*, not only the Gram staining, but also the form of the colonies and the behavior in the agglutination test, may vary greatly. *Hort* and his collaborators called the attention to the important fact that the smallest granular forms, produced by the meningococcus, are able to pass the Berkefeld filter. On "nasgar" plates minute colonies were grown from the filtrate, and in one well isolated colony the following cell forms were found: (*a*) Gram-negative diplococci (Weichselbaum's cocci), (*b*) small Gram-negative bacilli, (*c*) Gram-positive and Gram-negative cocci (Jaeger's cocci), (*d*) Gram-negative rods ("biscuit bacilli") with mostly Gram-negative, sometimes Gram-positive granules, (*e*) Gram-positive bacilli of unequal size. The apparent multiple spore-formation in, and the budding of the "giant" cells, was accepted later by *Hort* (1917 *b*) to be sufficient reason to remove this organism entirely from the bacteria and to place it among the Hemiascomycetes. As was mentioned on page 22, and will be more fully discussed in Chapter II, both processes are quite common with all bacteria.

H. Herzog (1913) has published another highly interesting paper upon similar observations made with *Neisser's* Gonococcus. Analogous changes between large and small (filterable) forms take place, which will be more fully discussed in Chapter II, their reproductive character being quite apparent. A reproduction of his figure 6, shown as figure 2 on Plate A, throws an interesting light on the relations existing between giant coccus-, dumb-bell-, and micro-forms, which *Herzog* also observed with meningococci.

In the genus Streptococcus irregular rod-, club-, and dumb-bell-shaped forms are also by no means rare. *Rindfleisch* (1872) probably was the first to observe directly under the microscope the breaking up of rods into globular forms and the melting together of streptococci to rods. *Billroth* (1874) discovered, by direct observation, that the lactic-acid streptococci are able to produce buds and clubbed rods. He distinguished the streptococci from the micrococci generally by their being inclosed in a cylindrical sheath, which was sometimes seen to be partially emptied. *Rosenbach* (1884) pointed out that size and staining quality of pathogenic streptococci may vary widely, even within the same chain. *Maddox* (1886) found clublike forms of *Streptococcus lactis* frequently in cultures one month old. An organism described by *Cornil* and *Babes* (1890, Vol. I, p. 506) as causative agent of an "endocardite ulcéreuse" seems to have been a rod-forming Streptococcus:

> Bâtonnets de 1μ d'épaisseur, de 2 à 3 ou 4μ de longueur, elles se disposent parfois en chaînettes; les bâtonnets se changent en diplococci ou en microcoques plus ou moins arrondis . . . Parmi ces chaînettes on trouve aussi des grains ronds colorés de la même façon, plus gros, de 1μ, 5 de diamètre.

Pansini (1890) recorded with various streptococci (his Nos. 4 and 5) large oval and rod-like "involution" forms. Two years later, however, in *Kruse* and *Pansini's* important paper upon the relationship existing between pneumococci and pyogenic streptococci (1892, p. 283) it is said concerning their bacillary forms:

> Involutionsformen möchten wir dieselben nicht nennen, im Gegenteil schienen sie in diesem Falle einem Excess im Wachstum ihren Ursprung zu verdanken, denn die Culturen gediehen viel besser als anfänglich.

All intermediate stages were seen, rods showing beginning segmentation, and also large yeastlike cells. The fact, clearly brought out for the first time in this paper, that pneumococci, as well as other pathogenic and nonpathogenic streptococci, can not be separated as true species, but must be looked upon as more or less stable varieties, occasionally passing over into each other, has since then found ample confirmation by publications of *Lemoine* (1896), *Lehmann* and *Neumann* (1912), *Baerthlein* (1912), *Rosenow* (1914), *Heinemann* (1915), and others.

Arloing and *Chantre* (1894) noticed that the rod forms, whose greater vitality *Kruse* and *Pansini* had demonstrated culturally, were also more virulent in the animal test; the French authors also observed the regressive metamorphosis from the rods to the streptococci, and they concluded therefore:

Il est probable que certains bacilles pyogènes ne sont que des streptocoques modifiés . . . Quand on trouvera des bacilles associés au streptocoque pyogène, il sera prudent de ne pas conclure nécessairement à une association microbienne.

The formation of clubs, branches, rods, large and small ovals, rhomboid bodies, apical growth, etc., with streptococci has been fully demonstrated by *Babes* (1895), who draws from his observations the following conclusion (p. 418):

Ich stehe nicht an, eine nahe Verwandtschaft besonders jener kurzen Streptokokken, welche häufig Kolben bilden, mit den Diphtheriebacillen und ähnlichen Bakterien zuzugeben.

His figure 2 contains so many interesting details, which undoubtedly will gain in importance, when studied more closely in further investigations, that a reproduction of it is given as figure 3 on Plate B.

That contrary to a widespread assumption the streptococci do not only divide transversely, but also longitudinally within the chain, was also discussed by *Babes* and indicated in his drawings. The same fact and its connection with the formation of branches was further emphasized by *Crookshank* (1896, p. 179), who also dwelled upon the variable size and form of the cells, especially of those at the end of the chain. Evidently not being acquainted with *Billroth's* early findings, he continues:

Another character which is very striking, may be seen when the individuals in a chain have become separated; an unstained or faintly stained membrane may be found bridging across the interval.

Such sheathed streptococci are also visible in *Babes'* sketches. They too furnish an interesting counterpart to similar sheathed granular forms produced by the Mycobacteria.

The *Streptococcus aggregatus,* isolated by Seitz (1896) from the mouth, was found to possess a wide pleomorphism of cells and of colonies. The latter were either small, looking like dewdrops or large, whitish, similar to the colonies of *B. pneumoniae,* or wrinkled and folded, like those of *B. mesentericus.* The size of the cells varied greatly. Regular "nests" were not rare, which contained all kinds of cocci, from the very smallest up to large "giant" forms, sometimes united in tetrades. Branching also was noticed. The globular forms changed into egg, onion, spindle, and lentil shapes, as well as into distinct short and long rod forms. All these various cells were sometimes present within the same chain. They were only partially Gram-positive. With this Streptococcus a diphtheroid organism was found in the mouth, whose cells and colonies remarkably resembled those of the Streptococcus.

A *Leuconostoc Lagerheimi* is, according to *Ludwig* (1896), dimorphous like *Leuconostoc* (Streptococcus) *mesenterioides,* viz., within the slime appearing as a regular Streptococcus, but when liberated, a motile short rod. *Beijerinck* (1898, p. 211), however, thinks that "*Leuconostoc Lagerheimi*" belongs actually to *B. xylinum Brown.*

The so-called *Micrococcus Sornthalii* of *Adametz* (1895), on the other hand, shows all marks of a true Streptococcus. On solid subtrates after some time large yeastlike cells became visible, which stained much better than the "normal" cocci.

Stolz (1898) found the large cells of pneumococci and pyogenic streptococci most frequently on serum agar. Rodlike forms, as well as clubs with short stems, singly or in short chains, were also present. Small cells and clubs showed often distinctly longitudinal division which led to branching, as was described before by *Babes* and by *Crookshank.* *Vincent* (1902) saw in pleuritic

exudate numerous bifurcate chains of streptococci, which continued growing in this manner when kept in a mixture of broth and human serum. Secondary branches were also formed, which, however, were very fragile like the others.

The slime-producing Streptoccoccus, which *Hlava* met in scarlatina, and for which the name *Leuconostoc hominis* was proposed by him, makes another excellent example of the relations connecting the streptococci and the diphtheria group. Some of *Hlava's* drawings, reproduced as figure 4 on Plate B, represent clearly all forms enumerated in the papers mentioned before. The transverse budding and branching, as well as the diphtheroid and yeastlike forms, are of special interest.

Thiercelin's Enterococcus is another example of a more thoroughly studied Streptococcus strain which exhibited all the various cell forms, characteristic of this group. In his first paper (1899) *Thiercelin* enumerates: Streptococci of very variable size, ovals with or without capsules, tetrades, staphylococci, short and long bacilli, and very large oval elements. He says:

> Ce microbe est doué d'un polymorphisme des plus remarquables et dans les cultures et dans l'organisme.

In his second paper (1903) the author reports that the very different forms abundantly present in old cultures continued to grow as such after being transferred to fresh substrates. On agar and in serum long threads, sometimes filled with granules, were also found. *Thiercelin* comes to the conclusion that the coccoid forms represent the young form of a bacillus:

> "L'entérocoque est la forme jeune d'une bactérie (entérobacille ou entérobactérie) . . . La forme d'involution semble être un effort fait par le microbe vers cette forme bactérie."

Michaelis (1902) discovered large accumulations of clubbed forms of streptococci in pleuritic exudate. Because he was unable to obtain any development from them on his substrates, he feels sure that they are "degenerate" and the beginning of "bacteriolysis."

In a diphtheria test *Ohlmacher* (1902) encountered a streptococcus of such peculiar behavior that a doubtful diagnosis concerning the diphtheritic or nondiphtheritic nature of the case resulted. In broth typical streptococci appeared. On Loeffler's serum, however, very polymorphous rods with clubs or swollen centers were seen, together with other forms, which looked very much like diphtheria bacilli. The author agrees with *Babes* that such growth of streptococci may cause mistakes in the diagnosis of diphtheria.

The pronounced rod form occasionally assumed by *Streptococcus lactis* was the cause that this Streptococcus as *Bacterium lactis acidi Leichmann*, or *Bacterium Guentheri Lehmann et Neumann*, has been wrongly placed in another genus, though its close relationship especially to Pneumococcus has been pointed out already by *Leichmann* (1900, p. 324), and then more fully by *Kruse* (1903) and by *Löhnis* (1907–1911). Its changes in morphology have been also discussed by *Düggeli* (1905) and by *A. Wolff* (1908), who found out that the presence of *B. putrificus* greatly enhanced the tendency of the lactic-acid streptococci to pass over into spindle-, dumb-bell-shaped, and otherwise diphtheroid forms.

The Streptococcus isolated by *Lorenz* (1909) from horses afflicted with "Brustseuche' gave also small and large coccoid cells, some of them growing very similar to *Staphylococcus pyogenes aureus*, fine rods resembling *B. erysipelatos suum*, and branched diphtheroid and Actinomyces-like forms. The appearance of the last-named type of growth was especially conspicuous in the presence of an Aspergillus, and it was most frequently noticed on the surface of solid substrates, while in their depth, as well as in liquid media, the typical streptococci persisted. The changes in morphology were accompanied by equally marked alterations in virulence.

Taddei (1909) tried *Streptococcus pyogenes*, *choreae*, and *erysipelatos* on different substrates (broth diluted with water, or broth mixed with 0.25–1 per cent tartaric acid or lithium chloride) and found that all his strains, though rather stable on ordinary broth, developed on the changed media to rods, very small and very large ovals (up to 6–7μ). These altered forms remained constant, except when brought back into ordinary broth. The morphological changes were accompanied by a speedy loss of virulence. That essentially the same effect was secured by diluting the broth as by adding the substances named is of special interest.

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In sugar media, used by *Broadhurst* (1915) in experiments upon the fermentative reactions of streptococci, also often considerable morphological changes became apparent. Rod-like, clubbed, pear-shaped, and obtusely diamond-shaped cells, as well as longitudinal dividing, were observed.

Mallory and *Medlar* (1916) say of their new *B. scarlatinae* that it approaches more nearly the strepto-pneumococcus group than the diphtheria group. It varies from coccus to long bacillary forms, grows best anaerobically, and is gram-positive. Its etiological significance remains to be studied.

Quite recently *Kraskowska* and *Nitsch* (1918) published some very good illustrations and a fairly complete description of the pleomorphism of streptococci, isolated from sick and from healthy persons. Their assumption that no such observations had been made before is, however, far from being correct.

The pleomorphous Streptococcus, which *Rosenow, Towne* and *Wheeler* (1916), *Nuzum* and *Herzog* (1916), *Rosenow* and *Towne* (1917), as well as *Mathers* (1917), consider to be the causative agent of poliomyelitis, a view which is not shared by *Amoss* (1917), *Bull* (1917), and others, shows once more the morphological changes characteristic to the streptococcus group. In this case the attention naturally was centered upon the production of minute, filterable coccoid forms, which, however, are by no means absent in the cultures of other streptococci. In this respect, too, the observations of the earlier investigators are in complete agreement with those of the authors named. Some of their photographs are reproduced as figures 9 and 10 on Plate I. For comparison one of our photographs of *Streptococcus lactis* (*Löhnis* and *Smith*, 1916 *b*) is added as figure 11, showing analogous differences in form and size. The picture of *Streptococcus tyrogenus*, reproduced as figure 12 on Plate I, was published by *Migula* (1900, Vol. II, Pl. I, fig. 2) as an illustration to his statement that the cells of this species are 2μ in diameter. The photograph, however, exhibits clearly large and very small forms, budding ovals and other details which were not mentioned by the author. The *Streptococcus equi*, reproduced as figure 13 on Plate II from another photograph of *Migula* (l. c., Pl. II, fig. 5) makes a very interesting counterpart to *Rosenow's* poliomyelitis picture.

It is evident that these observations will lead to discoveries of still more fundamental importance, especially when connected with those of *Herzog* and *Hort*, mentioned above. As the true character of these minute, filterable forms, however, seems to be more that of reproductive organs than of regular vegetative cells, the full discussion of their part in the life cycles of streptococci, micrococci, as well as of all other kinds of bacteria, will better be taken up from a general standpoint in Chapter II.

That the old form genus Sarcina is a rather hetereogeneous mixture of more or less similar cell forms, belonging to the life cycles of other organisms which are only partially related to each other, has been indicated above. Some sarcinae are obviously a special type of growth of various micrococci, as has been emphasized by *Lehmann* and *Neumann* (1912, p. 198) and others. The differences in the size of the cells are usually still more conspicuous than with micro- and streptococci, so that these authors explicitly state (l. c., p. 199):

> Angaben über Zellgrösse haben wir bei den Sarcinen nicht gemacht, weil wir hier besonders unregelmässige Resultate fanden. Es macht den Eindruck, als ob die Zellen oft gewaltig wüchsen und dann rasch hintereinander in acht Teile zerfielen.

Two copies taken from our second preliminary paper (1916 *b*) and reproduced as figures 14 and 15 on Plate II, may illustrate these differences in the cell form of *Sarcina flava*, when grown on beef agar 1 day and 3 months, respectively. Two others, figures 16 and 17 on the same plate, show the same organism after 6 days' growth in ammonium-citrate-glycerine solution. The breaking up of the larger forms into packages of small cells is fairly well discernible. The irregular outlines and the very dark staining of the large cells of fig. 16 are caused by their being newly formed from the symplasm, which process will be discussed in Chapter III.

Other sarcinae, however, will probably turn out, when studied more thoroughly, to be a special type of growth of various bacilli. *Beijerinck* (1901 *a*, p. 43, footnote) has already pointed out that *Miquel's* Urosarcina is no sarcina at all, but a bacillus, and a glance at the

drawing of *Urosarcina Hansenii Miq.*, reproduced as figure 6 on Plate C from *Miquel* and *Cambier's* Traité (1902, p. 628, fig. 172), confirms this standpoint. The Dutch author himself isolated some strains from soil which are said to represent intermediate forms connecting Sarcina and Bacillus Megaterium (l. c., p. 53, footnote). *Planosarcina ureae Beij.*, differing already from most other sarcinae by their ability to form endospores, is also distinctly inclined to produce small as well as large rods (*Löhnis* and *Smith*, 1916 *a*), though *Ellis* (1902) was unable to get a single rodlike cell with this or with any other sarcina.

As fig. 18 on Pl. II a photograph made by *Matzuschita* (1900, original fig. 6) is reproduced, showing the growth produced on salted substrates by a so-called *Bact. bruneum*, i. e. a brown variety of *B. fluorescens*. These cells have the typical appearance of regenerative bodies, yet they can be easily mistaken for sarcinae. A close study of *Sarcina mobilis Maurea*, the only organism within this group which is able to produce fluoresceine, might be of interest in this connection. *Lehmann* and *Neumann* (1912, p. 206) obtained the typical growth of *Sarcina tetragena* from an old culture of *Duclaux's Actinobacter polymorphus*. Contamination, of course, is also in this case not absolutely excluded, though not very probable. At least, there are too many parallels in the biological characters of *Sarcina tetragena* and of the *B. pneumoniae* group, to which Duclaux's Actinobacter belongs, to discard this finding lightly as contamination. *Ph. Eisenberg* (1914) noticed that also in mutation experiments *Sarcina tetragena* and *Bact. pneumoniae* resembled each other closely.

Figures 19–21 on Plate II are copies of some pictures of *Azotobacter vitreum*, published in 1914 as figures 22–24 in a paper by *Löhnis* and *Hanzawa*. This Azotobacter has a very firmly fixed tendency to show all morphological characters of a Sarcina. Yet it is no longer doubtful to me that this Azotobacter, like all others, is a type of growth of a spore-forming bacillus. But it was for the first time, after this strain had been under cultivation and observation for fully 10 years, that at least some large rods were produced and some inclination to form endospores became evident.

Billet (1890, p. 213) made the statement that all bacteria may appear as sarcinae by dividing themselves in three directions while in their "état zoogléique." This statement, however, is not sufficiently supported by facts. That, indeed, large packages of globular regenerative bodies may develop from the symplasm of every kind of bacteria, will be shown in Chapter III. But these irregular clumps bear, as a rule, only a slight resemblance to the typical sarcina forms, and it seems not to be a general rule that such "pseudo-sarcinae" are produced, as with *B. fluorescens* and *azotobacter*.

Sarcinastrum urosporae Lagerheim is another example of a bacillus with coccoid reproductive organs, which occur in packets like Sarcina. The rods, according to *Lagerheim* (1900) divide transversely and longitudinally, thus forming small cocci, which first increase in size and then germinate again to rods. Similar processes have been seen with other bacilli, e. g. with *Bact. Fraenkelii Hashimoto*, with *Matzuschita's* "proteusartigem Luftbacillus" and with *Bac. amylobacter* by *Bredemann*, to which we will have to refer on the following pages.

(b) NONSPORE-FORMING RODS.

Among the nonspore-forming rods the different *Proteus* varieties have been the first good examples of a distinct pleomorphism, morphologically as well as physiologically. It is true that *Hauser* (1885) at first made some concessions to the monomorphistic doctrine by creating three different species (*Pr. vulgaris*, *mirabilis*, and *Zenkeri*); few years later, however, he admitted that the differences existing between them were only sufficient to classify them as "physiological varieties" of one species. The typical forms, according to his description, are small cocci and short rods (0.4–0.6 × 0.9–1.2 μ). But there were also present in young cultures large rods and threads (1 × 7.5–37.5 μ), large round cells (of 1.6 μ diameter), well developed spirals (with 2–4 turns), long twisted "spirulines," and large pear and club shaped so-called involution forms (3–7 μ), which, however, were actively motile, multiplied as such, and were replaced in old cultures by the "normal" small rods and cocci.

Proteus fluorescens, discovered by *Jaeger* (1892) as a causative agent in Weil's disease, shows otherwise all morphological and cultural characters of this group, but produces fluoresceine. *Kohlbrugge* (1901) met with an interesting symbiosis of a proteus-like rod and a vibrio in feces. Both grew better when united, and the vibrio simulated the rod in its different forms (cocci, short rods and waved threads) to such an extent that only single-cell cultures secured the final decision. The *Bacillus proteus denitrificans of Höflich* (1902) furnished always at first long thin threads with pointed ends ($0.3–0.4 \times 20–100\ \mu$); they divided into long rods ($5–10\ \mu$) and spirals, these into short rods and vibrios, at last coccoid and yeastlike forms appeared. All short forms reproduced long threads after each transfer. On account of its having several polar flagella *Lehmann* and *Neumann* (1912, p. 428) are somewhat in doubt, whether it really represents a Proteus form. Possibly the same dimorphism in flagellation (polar and peritrichous) occurs here, as it does with *B. coli*.

The "proteusartige Luftbacillus," briefly described by *Matzuschita* (1902), deserves our special attention not only because of its inclination to longitudinal fission, but still more because the various "involution" forms, as shown in the reproduction of some of *Matzuschita's* drawings in figure 5 on Plate B, will prove to be of special interest, when viewed (in Chap. II) in the light derived from other observations on hitherto very little known reproductive processes in the life history of the bacteria.

Under the designation "*Bacterium pyogenes ramosum*," *Stefansky* (1902) added another so-called species to the Proteus group, which in the pus from an abscess of the skin showed exclusively the form of a coccus, while on the plate nothing but short rods became visible. They produced within 24 hours longer rods and threads with spindle- and club-shaped inflations, in broth large globules also, and Y-forms. On agar containing 5 per cent NaCl the highly pleomorphous picture, presented already by the other forms, became still more complicated by the presence of ring-shaped, spirilla and spirochaete-like forms, as well as of branched cells.

Bacterium Zopfii, described by *Kurth* (1883) two years before *Hauser* published his monograph on Proteus, is closely related to Proteus Zenkeri, as I have shown (1905 *a*, p. 720) by a comparative study of a number of varieties. *Kurth* was not able to obtain a multiplication of the cocci as such. They always reproduced rods, and were therefore considered by him to be resting forms. They originated by fragmentation of the rods. *Schedtler* (1887) confirmed these findings by direct continuous microscopic studies. He also saw branched spirals.

Whether *Bacterium merismopedioides* of *Zopf* (1883) belongs to this group can not be decided, as only insufficient data are available. Its breaking up into cocci, forming tetrades and sarcina-like arrangements, as shown in fig. 7 on Plate C, indicate, however, a morphological relationship to *Bact. Zopfii Kurth*, as well as to Matzuschita's protean bacillus from the air. *Zopf* saw motility of the "cocci", whereas those of *Bact. Zopfii* were found to be immotile.

The Lactobacilli furnish many more details, which do not fit the monomorphistic theory. Long slender rods are typical, but short rods and cocci are by no means rare, and branching can be observed so readily that some investigators not only discussed the relations connecting lactobacilli and actinomycetes, but directly transferred the lactobacilli into the last-named group. *C. Sternberg* (1898) is one of the few authors who claims to have seen motile lophotrichous rods of the Boas-Oppler bacillus. The same author also recorded clostridia, plectridia, and regular endospore-formation. (See Chap. II.) The two best-known lactobacilli from the intestinal tract, *Bacillus acidophilus Moro* (1900) and *B. bifidus Tissier* (1900), are both very much inclined to exhibit the characteristic branching. *Moro* found water cultures very useful for this purpose. So-called degeneration forms (ring, club-shaped forms, spirals and others) were frequent on agar after a few days. Some of *Tissier's* drawings, reproduced as figure 8 on Plate C, show many features to be found with *B. radicicola* and other members of the *B. pneumoniae* group. That there are connections linking the lactobacilli on the one side with these organisms, and on the other side with the streptococci, has been discussed in my paper on the lactic acid bacteria (1907). *Tissier* (l. c., p. 91) declares the "formes vésiculeuses" to be signs of degeneration. But it seems more probable that they represent a special intermediary step in the life cycle of this organism, as well as of others, e. g. with *B. pneumoniae* (see *Toennies*-

sen's findings below). Branched forms are, according to *Tissier*, frequent in feces, on good substrates after they are somewhat exhausted or have turned acid, and often under the influence of symbiosis with other bacteria. Just as with *B. radiciola*, the three ends of a Y form are not infrequently the only parts which take the stain, and which are able to give further development.

Another strain of the Acidophilus type, isolated by *Cahn* (1901), was given the special name "*B. aërobicus ramificatus*" on account of its abundant branching. *Rodella* (1901) found the pleomorphism of this group so bewildering that he was unable to decide whether the different strains studied by him should be given species or only varietal character. When treated with the Gram method, the rods behaved very much like diphtheria bacilli, showing gram-positive and gram-negative parts. Continued investigations led to the conclusion (*Rodella*, 1908) that practically all lactobacilli from the stomach (Boas-Oppler bacillus, *B. gastrophilus*, *acidophilus* and *bifidus*) are merely representatives of one single species. *Blühdorn* (1913), on the other hand, vigorously maintained that there be no similarity whatever between the two last-named bacilli; they are said to be entirely different, morphologically as well as physiologically. Undoubtedly both extreme views are incorrect. There is neither a complete identity, nor an absolute nonidentity. All lactobacilli together form a natural group, and not before their full life history is known, we will be able to say, whether it is made up of different species or only of a chain of varieties. At present, the latter view seems to be more probable. What surprises are still in store for more thorough investigations is indicated by the discovery made by *Noguchi* (1910), that *Bac. bifidus* is "an anaerobic phase of life of an aerobic sporogenous organism . . . closely resembling *Bac. mesentericus fuscus*." *Noguchi* was able to complete experimentally the transformations both ways. *Sandberg* (1904) who also saw motility, made some important observations upon the correlations existing between the different variable types of colonies and the form of rods, produced by the "long bacilli" from the stomach.

The lactobacilli in milk, cheese, and other fermented food, exhibit the same instability of appearance when growing under different conditions. Besides the "normal" slender rods, long threads with inflations, as well as chains looking very much like streptococci, are equally frequent. *Henneberg* (1901), *Holliger* (1902), *Freudenreich* and *Thöni* (1905) and many others have furnished valuable information upon these organisms, which was collected some years ago in my papers on lactic acid bacteria (1907, 1911). From our present standpoint the following publications are of special interest: *Düggeli* (1905) and *Weigmann*, *Gruber* and *Huss* (1907) on the organisms in the Armenian sour milk (matzoon); *Rubinsky* (1910) upon the koumiss bacterium; *Chatterjee* (1910) on the lactobacillus (mistaken by this author for a Streptothrix) in the fermented milk of British India, called dadhi; *Heinemann* and *Hefferan* (1909) and *Koegel* (1914) on the bacillus from Bulgarian sour milk (yaourt), usually, though wrongly, termed *B. bulgaricus*. Undoubtedly the polymorphism of this group surpasses by far that of Proteus, and is perhaps even more pronounced than that of the plague bacillus and of the diphtheria group. Starting from the short, coccoid and club-shaped cells, practically all intermediate forms may become visible up to the very thin threads with pointed ends, sometimes only 0.2–0.3 μ thick, not infrequently waved and coiled, and often branched. The plates attached to the papers of *Weigmann* et al. and of *Rubinsky* may be consulted for good illustrations.

Among the organisms of this group *Bact. acidi propionici b* of *Freudenreich* and *Jensen* (1906) is perhaps the best example thus far known, exhibiting marks of relationship between the lactobacilli and the diphtheria group. At room temperature appearing as a small short rod ($\frac{1}{2} \times 1\mu$), it becomes a long rod at 37° C., forming clubs which stain like the barred type of the diphtheria group. Granules showing the *Neisser* reaction may be found occasionally with all lactobacilli. The "Körnchenbacillen" of some German authors can not be accepted as a special type.

That at least some of the old, poorly described Leptothrix forms are to be classified with the lactobacilli can hardly be doubted. In some of the early publications of *W. Miller* (1882–1889) the pleomorphism of this group has been already fairly well indicated, though, of course, no definite information can be gained from these necessarily very incomplete investigations.

Bac. funduliformis Hallé (1898, pp. 28–31) and some other anaerobic nonspore-forming bacilli seem also to be naturally related to the lactobacilli, especially to those displaying a distinctly anaerobic character. On the other hand, they are also related to anaerobic spore-forming bacilli. The same, however, holds true for the lactobacilli, as will be more fully discussed in Chapter II. *Hallé's* vaginal bacillus grows in the pus as a slightly curved thin immotile rod, but in the cultures a conspicuous pleomorphism was noticeable, as illustrated in figure 9 Plate C (from original fig. 3). Large rods and threads, with inflations, branches, buds, clubs, balls, etc., were formed; in the animal tests oedema and gangrene were caused.

An anaerobic bacterium, found by *Ghon* and *Sachs* (1905) to be connected with peritonitis, and either identical or closely related to *B. funduliformis*, gave also prominently small immotile rods, slightly longer and thicker than the influenza bacillus, accompanied by cocci, threads and inflated forms, when taken from the exudate. In the cultures the pleomorphism became more enhanced by the presence of thick waved threads, club- and pear-shaped cells, ovals, yeastlike, and spindle forms, all of which were Gram-negative, and whose development was stimulated by adding 1 to 2 per cent glucose to the substrate. *Kisskalt* (1906) studied a similar organism, isolated from an abscess, and emphasized its relationship to the Streptotrices. Three other small Gram-negative anaerobic rods, isolated from meningitis by *Ghon*, *Mucha* and *Müller* (1906) are also to be included in this group. They are either identical or closely related with each other. Their appearance after 4 days growth at 37° C. is illustrated in figure 10 on Plate C (reproduced from original figs. 6, 9 and 20).

Several other organisms found in cases of typhus exanthematicus, whose etiologic significance is still more or less questionable, are also to be mentioned here. The immotile diplobacillus of *M. Rabinowitsch* (1909), showing bipolar staining, and the organism described by *P. Th. Müller* (1913), are apparently either closely related or even identical. In the blood they appear as cocci, diplococci, and short rods; but in the pericardial liquid large globules, ovals, yeast like and big dumb-bell or club-shaped cells occur. The figures reproduced as Nos. 22–24 on Plate II (from original figs. 2, 5, and 1, respectively) show coccoid forms from gelatin, 2 days old, rods from glycerine agar, 2 days old, and so-called degeneration forms from serum broth, 8 days old. The latter especially indicate relations to the mycobacteria. In their paper upon the diphtheria group *Trautmann* and *Gaethgens* (1913) have published a photograph (fig. 8, p. 72) demonstrating exactly the same type of clubs, cocci, and short rods. Gram staining was either positive or negative with *Müller's* organism. *Plotz, Olitzky* and *Baehr* (1915) also isolated a pleomorphous, Gram-positive, small bacillus from typhus cases, which grew either as a coccus, or as a short straight or curved rod, and which was very much inclined to produce, in young cultures, so-called involution and degeneration forms. The authors use these expressions, though they found that these special forms can be made constant by frequent transfers, which fact undoubtedly does not fit their assumed "degenerate" character. The filterability of the typhus virus is not admitted by these authors. However, here as in other cases the observations of *Hort* (1915) seem to be an important step toward the solution of the problem. It is very probable that his small Gram-positive or Gram-negative filterable organism is nothing else than the gonidial stage of the pleomorphous rod found by the other authors. In Chapter II this point will be more fully discussed.

B. erysipelatos suum, *B. murisepticum*, and *B. erysipeloides*, considered by *Rosenbach* to be different, while other authors accept them as identical (see *Lehmann* and *Neumann*, 1912, p. 430), furnish another prominent example against the monomorphistic theory. First described by *Rosenbach* (1884) as micrococcus, soon after, however, declared by him (1887) to be neither a micrococcus, nor a bacterium, nor a bacillus, but an organism of peculiar systematic standing, perhaps related to Cladothrix, it has been more recently studied anew by the same author (1909), whereupon it was made the type of a new genus Erysipelothrix. Four of the photographs accompanying the last-named paper have been reproduced as figures 26–29 on Plate III. Figure 26 (original fig. XIII, 5) represents *B. erysipeloides* from blood serum, 7 days old. Figure 27 (original fig. XII, 5) shows the same organism from broth, only 9 hours

old; branching, terminal swelling, as well as budding, are clearly visible. Figure 28 (original fig. XIII, 3) demonstrates a spiral form of *B. murisepticum* in gelatin, and figure 29 (original fig. XII, 3) a thin mycelial growth of *B. erysipeloides* from a 6-weeks-old gelatin culture, resembling very much a similar development of lactobacilli (shown e. g. in *Rubinsky's* koumiss paper). Another picture of *B. erysipelatos suum*, taken from the "Atlas" of *Itzerott* and *Niemann* (1895, fig. 40), has been added for comparison as figure 25 on Plate III. That also in this case very different cell forms, as well as budding, are easily discernible, demonstrates sufficiently how difficult it is to get "legitimate" monomorphous material; for it may be safely assumed that the authors have selected a field as uniform as they could find. As early as in 1889 *Karlinski* introduced a "new pathogenic schizomyces" under the name *Bac. murisepticus pleomorphus* into the literature, which already clearly exhibits most of the marks mentioned by *Rosenbach* 20 years later as characterizing his Erysipelothrix. *Karlinski* emphasized the protean nature of his bacillus. The short rod was considered to be typical, but "nearly all forms became visible, from small, globular and oval cells up to slender spirals," and in old cultures "terminal swellings appeared, often five times as thick as the rods and threads," which the author felt "compelled" to classify as "involution" forms. That under special conditions, as mentioned on p. 40, *Lorenz* (1892) obtained an actinomyces-like growth of *B. erysipelatos suum* is quite in line with these other findings. And it is very probable, too, that the "Streptothrix" growth which *Kitt* (1897) found in his "Rotlauf" cultures, when kept in serum broth, was not a contamination, as he later (1898) assumed, but really the analogous type of growth, as in the other cases. (See also p. 20.)

B. septicaemiae haemorrhagicae has been represented in the "Atlas" of *Itzerott* and *Niemann* (1895, fig. 36, "Hühnercholera") by the photograph reproduced as fig. 30 on Plate III. It is certainly not easy to understand how the authors actually photographed unknowingly something quite different from the typical bipolar rods, which they undoubtedly intended to show. Evidently they were so well trained to see only "bipolar rods" that all the single globular bodies, their budding (in the center of the picture), and their Staphylococcus-like arrangement were passed unnoticed. It is a good example of well-developed regenerative bodies, photographed but not seen. A comparison with figure 18 on Plate II (regenerative bodies of a Fluorescens variety) might be recommended. *Rosenfeld* (1901) noticed that the addition of salt stimulated the formation of ring-shaped, globular, thread-like, and branched cells in the septicaemia group as in others. *G. Phisalix* (1902) found the mycelium-like growth of Pasteurella in the body, while in the cultures the cocco-bacillary form reappeared; the virulence was the same in both cases. *Bang's* abortus bacillus has been classed by *Nowak* (1908) as a pleomorphous member of the septicaemia group, showing coccoid, branched, and various other forms, but it seems more correct to place this organism among the mycobacteria. *Klepzoff* (1912) succeeded in getting acid-fast growth from septicaemia organisms in the course of experiments, which led to the discovery of relations existing between *B. tuberculosis* and *Pasteurella* groups.

B. pseudotuberculosis rodentium has been studied by *Galli-Valerio* (1903) and *Zlatogoroff* (1904) in regard to its pleomorphism and its relation to *B. pestis*. Very similar small and large as well as branched cells were found to be frequent with both organisms. A "new species" *Bacterium pseudopestis murium* described more recently by *Galli-Valerio* (1913) may be also accepted as an aberrant strain of *B. pseudotuberculosis rodentium*. Its plague-like pleomorphism deserves full attention with respect to the plague diagnosis.

The wide variations in the microscopical appearance of *B. pestis* have been made the object of numerous studies; those of *E. Klein* (1897) upon the correlations existing between cell forms and colony types of *B. pestis* apparently being the first of its kind. A very detailed report upon plague morphology has been furnished by *Albrecht* and *Ghon* (1900). The reproductions of a few of their drawings, given in figure 11 on Plate D, present a good illustration of the very wide pleomorphism characteristic for this organism.

Coccoid forms are considered to be the initial type of growth. They pass over into the short rods showing bipolar staining, and therefore occasionally looking like diplo- and streptococci. Later the cells increase in size, some swelling up to yeast-like, pear-, club-, or spindle-

shaped appearance, others stretching out into threads, which sometimes show branching or a conspicuous swelling in the center. All these forms are present in the body, as well as in the cultures. That the large cells are no "involution" forms, is not only proved by their vitality, but still more by the fact that in several months old cultures the coccoid forms exclusively are to be found. Budding and branching is frequent after not more than 48 hours on glycerin agar. *Skschivan* (1900) saw it in only 1-day-old growth, and he is therefore inclined to place the plague bacillus among the actinomycetes, next to *B. mallei*. *Dieudonné* (1903) calls again all forms surpassing the "legitimate" coccoid or short-rod type, "involution or degeneration forms," though they are, according to his own statement, fully virulent, present already in the bubo after a short time, and most frequently obtainable in fresh isolations from the animal. Figures 31–33 on Plate III are reproductions from the textbook of *Muir* and *Ritchie* (1903). Figure 31 (original fig. 148) shows the so-called normal coccoid and rod-like cells from a young agar culture, figure 32 (original fig. 150) the "involution" forms from 4 per cent salt agar, and figure 33 (original fig. 147) the microscopical appearance of the organisms as taken from the tissue. There is unquestionably much likeness between figures 33 and 32, but hardly any between 33 and 31.

The difficulties occasionally arising from the microscopical similarity of *B. pestis* and *B. pseudotuberculosis rodentium* have been discussed by *Galli-Valerio* (1903) and by *Zlatogoroff* (1904) in papers referred to above. The conditions favoring one or the other type of growth have been the object of special studies by *Cacace* (1903). Long and sometimes branched Streptothrix-like threads were e. g. easily obtained in broth, containing 0.01–0.05 per cent potassium chromate, while the addition of 0.5–1.5 per cent carbolic acid to the broth stimulated the growth of cocci, which equally predominated on gypsum plates saturated with broth. Abundant and uniform branching was secured by *Kodama* (1908) with 10 strains of *B. pestis* when these were cultivated on coagulated egg albumen. *Gotschlich* (1906) reported upon an avirulent plague "mutation" which grew in smooth, circular colonies, but reverted in two of three cases to the original type, after having been kept for two months in the icebox. *Rowland* (1912) was able to transform experimentally the plague bacillus into a strain showing all characters of *B. pseudotuberculosis rodentium*. In another paper he states that "probably no organism presents so marked a pleomorphism as the bacillus of plague," and he demonstrates this by a large collection of beautiful photographs, two of which are reproduced on Plate III: Figure 34 (original fig. 12, Pl. XIX) mycelial growth in immune serum, and figure 35 (original fig. 17, Pl. XXI) yeast-like cells from the seat of inoculation in the rat. The correlations existing between cell form, virulence, and appearance of the colonies have been studied anew by *Markl* (1914). Highly virulent, freshly isolated strains gave small thin colonies, while others, more or less reduced in virulence by prolonged cultivation on artificial substrates, produced large succulent colonies. The single cells, however, were larger and thicker in the virulent than in the saprophytic strains. An entirely avirulent pseudo-plague bacillus from the soil, which I described (1905 *b*) under the name *Bact. agreste*, exhibited a surprising similarity to the true plague bacillus, morphologically as well as physiologically, but differed from it by being, at least temporarily, actively motile.

The various cell forms of *B. influenzae* have been demonstrated by *Crookshank* (1896) in the drawing reproduced as figure 12 on Plate D (from original fig. 122). The filaments are composed of long and short rods, coccus forms of different size, and of irregular elements. According to *Grassberger* (1898) the latter are present especially in luxuriantly growing cultures. Thick wedge-, spindle- and club-shaped cells are produced. True branching also was observed and photographed. On horse serum all 40 strains tested developed uniformly very long threads, which occasionally showed one or more inflations. *D. J. Davis* (1907) found that also in this case the presence of 2–3 per cent sodium chloride in the substrate stimulated the tendency to pass over into irregular large forms, somewhat resembling the diphtheria organism. But these alterations were not thought by him to be characteristic.

A very remarkable polymorphism has been described by *Waelsch* (1905) for his *B. involutus*, which *Lehmann* and *Neumann* (1912, p. 274) place close to the Morax-Axenfeld conjunctivitis

bacillus, but which also shows signs of relationship to the *B. pneumoniae* group. Very different forms were already present in the colonies. After a few days' growth representatives of practically all of *Cohn's* form genera appeared in the field. Figure 13 *a* on Plate D is a reproduction of the original figure 4, showing the development on glycerin agar after three days. Figure 13 *b* (original fig. 6) gives the picture of a 5-days-old broth culture.

Among the species or varieties belonging to the group of *Friedländer's B. pneumoniae* the so-called *Proteus hominis capsulatus*, as described by *Bordoni-Uffreduzzi* (1888 *b*) represents a form which in regard to its pleomorphism comes very near to *B. involutus Waelsch*. Besides the cocci, rods, and threads, which are characteristic for the group, and large globules acting as reproductive organs, very different spindle-shaped, curved, and triangular forms became visible on potato, which might be easily mistaken for "degenerate" spirilla. Figure 14 on Plate D (a reproduction of original fig. 3 on Pl. VII) shows them, as well as some branching. As the author explicitly says, they are no "involution" forms, because they are formed when the development is at its height, and they are replaced by the simpler forms when the culture grows older.

The *B. mucosus* isolated by *Simoni* (1900) from ozaena is another interesting example of the pronounced pleomorphism of the *B. pneumoniae* group. In the body typical cocci predominated, while in the cultures, especially on solid substrates, the bacilli came to the foreground. At the same time, however, so many other forms were already visible in young cultures, that only by repeated experiments full certainty about the absence of contaminations could be secured.

The "new species," isolated by *Jehle* (1902) from sputa in different cases of pulmonar affections, possesses all marks of Friedländer's bacillus. Cocci pass over into short rods, these stretch out into long, thick, often curved threads, which eventually exhibit spindle-shaped or globular inflations. All these various forms are present in cultures not older than 2–3 days. *Sachs'* "Kapselbacillus" (1903) displayed practically the same pleomorphism.

B. Berestnewi of *Lepeschkin* (1904) should probably also find its place here, according to its origin (sputum from a pneumonia case) and its general morphological and cultural characters. It produced the typical round, white, soft colonies, but was avirulent. The change between cocci, rod-like, and thread forms followed the common lines, though the size of the cells was larger than usual, and there was a very pronounced tendency to produce branched rods and threads. This tendency could be increased and stabilized in single-cell cultures, and it was much more noticeable with young than with old material. My own investigations (1905 *a*, p. 587) revealed very clearly that all members of the *B. pneumoniae* group are easily induced to display their ability of forming branches (so-called bacteroids). *Péju* and *Rajat* (1906 *c* and *e*) found potassium iodide, as well as urea, especially useful for stimulating the characteristic changes in appearance; 1–2 drops KI favored the development of very large round cells (of 3 to 4 times the normal size), while 10 drops increased the formation of long threads.

Some very interesting work upon the transformation of the large encapsulated ovals, not infrequently seen with the Friedländer bacillus, into slender small coli-like rods, has been done by *Toenniessen* (1913–14), who accepted these changes as "mutations," though they evidently represent different stages in the life history of this organism. Six of his photographs (Nos. III–VIII) are reproduced as figures 37–42 on Plate IV. The irregular intermediate forms, in which the chromatine granule only takes the stain, deserve our special attention. They, too, indicate the relationship existing between *B. pneumoniae* and *radicicola*. Their exact place in the life cycle of members of this group will have to be discussed in Chapter III. The thin coli-like rods proved to be entirely avirulent, but they reverted to the original short virulent type, when transfers were made from 6–8 weeks old cultures. The *Coccobacillus foetidus ozaenae Perez*, recently studied by *H. C. Ward* (1917), furnishes another example of the pleomorphous nature of this group. Besides the well-known differences in shape and size of the cells, variations in the motility were observed. Some strains remained permanently immotile, while others gained motility, thereby indicating, also in this respect, their tendency to approach the Coli type. That in old cultures a dark brown pigment became noticeable, is not surprising in

view of the fact that the same behavior is often ascertainable with typical strains of *B. pneumoniae.*

Two highly pleomorphous organisms, both probably related to *B. coli,* have been isolated in a case of oedema by *Harris* (1893). One showed a brownish, the other a pink color; the former was pathogenic, the latter was not. Both of them produced at first cocci and diplococci, which later developed into paired stout rods (1×4–6μ), or thin long rods and threads (0.5×4–12μ), respectively. Sometimes the pink organism exhibited distinctly Leptothrix-like forms. Budding and branching are also shown in the photographs accompanying the paper, but there is no word about them to be found in the text. In a paper entitled "The Pleomorphism of the Common Colon Bacillus," *Haslam* (1898) discussed the influence of quality and quantity of nitrogenous food upon the length and the width of the cell form. *Adami, Abbott,* and *Nicholson* (1899) discovered in cirrhotic, and also in normal, livers of men and animals minute spherical or oval bodies, which could be easily mistaken for pigment granules in the liver cells, occurring singly or in pairs, sometimes in strings of three and four, which on artificial substrates produced small colonies quite different from those of *B. coli.* Yet successive transfers led back to the typical colony and cell form of *B. coli. M. E. Abbott* (1900) has published some more data upon these investigations, to which reference will be made in Chapter II. Cultivation of *B. coli* on salt agar furnished *Matzuschita* (1900) large monstrous inflated threads. Figure 36 on Plate III is a reproduction of his figure 14. Another Coli strain gave large globules. Both forms are, as will be shown in Chapter II, of the same physiological value. *W. Winkler* (1900) observed granulated spindle-shaped "swarming bodies" of *B. coli,* which are probably of the same rank as analogous forms discovered by *Matzuschita* as a type of growth of his protean bacillus from air (fig. 5 on Pl. B). *Ohlmacher* (1902) isolated from a colon bacillus septicaemia a highly pleomorphous coli strain which only after several transplantations ("rejuvenation") in broth assumed again the "typical" behavior. "All gradations from minute coccoid or diplococcoid to long coarse filamentous forms were observed." Other threads were quite thin and shadowy. Some contained a row of deeply staining inclusions. Others in young cultures made from heart's blood showed lateral buds and short true branches. Some of the rods and filaments had median swellings, others clubbed ends. According to *Prell* (1917) *B. coli* may live in a "rhabdocytic" and in a "coccocytic" phase, and other bacteria may grow in a similar manner.

Walker and *Murray* (1904) discovered that 0.2 per cent saturated alcoholic solution of methyl violet added to agar, broth or gelatin, caused typhoid and coli bacilli to grow in long undulated, sometimes very thick, threads, which showed true branching and segmented in old cultures into chains of cocci. The authors expressed the belief that these alterations indicate "an unexpected complexity in the life history of these microörganisms." Data to be given in Chapter II will prove the correctness of their assumption. *Péju* and *Rajat* (1906 *b* and *e*) obtained analogous results by adding potassium iodide or urea to their substrates; and these were confirmed by other tests with urea made by *Wilson* simultaneously (1907). *Revis* (1912 *a*) succeeded, by making use of malachite green, in changing one of three Coli strains to such an extent that it now was "neither physiologically, morphologically, nor culturally a colon bacillus." It produced slime and grew in long filaments or as very short rods. The same author also studied (1912 *b*) the coccoid forms of *B. coli* and came to the conclusion that relations seem to exist with Gram-negative micro- and streptococci, analogous to those connecting Gram-positive streptococci and Gram-positive rods producing lactic acid. *Lehmann* and *Neumann* (1912, p. 256, footnote) observed occasionally that a monotrichous Coli strain became peritrichous, and the opposite change was recorded for *B. alcaligenes faecalis,* which first was described to be peritrichous, later monotrichous (*Lehmann* and *Neumann,* 1912, p. 357). When *Pollak* (1913) cultivated this organism on Dieudonné's blood agar, he obtained cholera-like colonies, and the rods appeared like vibrios. On the other hand, several vibrios have been found to be inclined to assume coli-like growth, as will be discussed later. Special investigations upon the natural relationship which seems to exist in this direction, might lead to very interesting results.

Some pictures, shown by *Kellerman* and *Scales* (1916) as illustrating certain phases in the life cycle of *B. coli,* are reproduced as figures 43-45 on Plate IV. Figure 43 makes an interesting counterpart to the preceding pictures of *B. pneumoniae.* The clusters of large globules and the hyphae-like threads in figure 45 represent forms whose physiological significance will be discussed later. The small unstained thread containing four chromatine granules (in the lower left part of fig. 44), also deserves our attention. Similar pictures of *B. coli* published by *Hort* (1917 *a*) will find their place better in Chapter II (Pl. XIII, fig. 180), as they are especially suited for explanatory purposes. The same holds true in regard to other data upon the behavior of the typhoid and dysentery organisms, contained in the same paper, and also in regard to drawings of *Meirowsky* (1914 *b*) illustrating similar phases in the life history of *B. paratyphosus B.*

Matzuschita (1900) published a photograph of the typhoid bacillus grown on salt agar which is reproduced as figure 46 on Plate IV (from original fig. 16). It should be compared with figure 36 on Plate III, showing the development of *B. coli* under analogous conditions. Other examples of true branching are to be found in a photograph of *B. typhosus* published by *Itzerott* and *Niemann* (1895) in their "Atlas" (original fig. 18), reproduced as figure 47 on Plate IV. The material used in this case, was taken from an agar culture. *Gamaleia* (1900) studied the peculiar effect exerted by lithium salts. Large globules and branched forms became very frequent. That these and other alterations of the cell form are not merely passive, osmotic reactions, as was later assumed by *Loeb* (1902), has been already emphasized by *Gamaleia* (l. c., p. 211). *Casagrandi* (1901) found cultivation on gypsum plates very useful for developing the branched growth of *B. typhosus.* *Walker* and *Murray* (1904) attained the same result by adding 0.2 per cent alcoholic methyl violet solution to agar, gelatin or broth, while *Péju* and *Rajat* (1906 *a*) and *Rajat* and *Péju* (1906) were only able to induce the typhoid bacillus, when treated with potassium iodide, to produce long immotile threads showing oval, pear- or spindle-shaped inflations, but no branching. In old cultures fragmentation of the long forms into short rods and coccoid forms was frequently observed. Urea agar furnished *Wilson* (1907) analogous, filamentous, round, and swollen forms, and also true branching. As early as in 1893 *Almquist* had pointed out that *B. typhosus* not only multiplies by fission, but also by producing lateral round buds which grow up to new rods. Later (1904) he added, that also very thin needle-like rods may directly come out from the old rods. These, as well as his other findings concerning the reproduction of the bacteria will be considered more specifically in Chapters II and III. *Bernhardt's* (1915) studies "upon the variability of pathogenic bacteria" confirm the earlier findings of thick immotile threads being formed by *B. typhosus* in old cultures, which still later break up into normal motile short rods; in a few cases, however, motility was lost permanently.

That occasionally paratyphoid strains can assume all marks of the true typhoid organism, and vice versa, has been shown by *Köhlisch* (1918) and by *Baerthlein* (1918). The first named author also reported (1916) upon some interesting yellow variants of the typhoid-paratyphoid group.

Valuable results with dysentery bacilli were secured by *Hata* (1908) when he studied the so-called "degeneration" forms of *B. pestis, typhosus, dysenteriae, coli,* and *cholerae,* produced on agar containing various amounts of $CaCl_2$, $MgCl_2$, or NaCl. Dysentery organisms were the only ones which "degenerated" already on 1 per cent $CaCl_2$ agar, i. e., the thin cells became larger and longer, and with increased salt content they assumed giant spindle forms, Some strains furnished in addition large globules. True branching was frequent on NaCl agar. Disappearance and reappearance of motility in dysentery strains have been discussed in a paper by *Dunn* (1904). The experiments of *Péju* and *Rajat* (1906 *d* and *e*) with potassium iodide and urea gave results analogous to those mentioned before. Inflated threads and globules were produced, which later partially broke up into normal short rods. Data concerning the correlations existing between different cell forms and appearance of the colonies in the typhoid-dysentery group are to be found in *Baerthlein's* (1912) report on "mutation" among bacteria.

The acetic acid bacteria are demonstrating their close relationship to the pneumonia-colon group, as in other directions, so also by their inclination to form the same type of large globules

and inflated threads, which later reproduce the small "normal" forms. But it is very characteristic that in this special case the large forms, though put aside in all other cases without any adequate test as uninteresting "involution forms," have been generally accepted in the textbooks as some important peculiarity of the acetic acid bacteria, because in this case a well-known investigator, *E. Chr. Hansen* (1879), before the monomorphistic doctrine took possession of most of the bacteriological textbooks, has pointed out that they belong to the normal life cycle of these organisms. He also observed directly (1894) their formation and their segmentation into small rods in single-cell cultures of *B. aceti* and of *B. Pasteurianum*. Figure 15 on Plate E is a reproduction from his first paper (now fig. 77 on p. 458 in his "Gesammelte theoretische Abhandlungen," 1911). *Lafar*, on the other hand, was at least for some time of the opinion that the large forms should be considered to be "pathologic deformities," because he noticed that increased acidity stimulated their development. However, an acid substrate is the natural habitat of these organisms, and their development is at its height under such conditions. *Zeidler* (1896) described a motile acetic acid bacterium, also representing the characteristic threads and inflations. *Henneberg* (1897–1898) created numerous "new species," which all showed the same character. He emphasizes the diagnostic importance of their "hypertrophism" and pays special attention to those lateral buds which are produced by the acetic acid bacteria in the same manner as by the lactobacilli. They appear on beer after two days and at temperatures as low as 26–29° C. *Kruse* (1910, p. 1126) admits that the luxurious growth on natural substrates is made up by the large forms, while the poor growth on artificial media shows only small short rods; and yet he still calls the former "quaint involution forms." In a special study upon this group *Janke* (1916) introduces the new term "aberration" forms, though he accepts them at the same time as part of the "normal" life cycle of the acetic acid bacteria, which, therefore, if these authors were right, would be "normally aberrant" or "normally degenerate" while growing luxuriantly under natural conditions.

Some of the so-called photobacteria form another interesting branch of the *B. pneumoniae* group. Their characteristic pleomorphism has been well illustrated in a little known paper by *Barnard* (1899), as well as in the more often quoted publications of *Molisch* (1903–1904). *Reinelt* (1905) has added other details; cocci and rods were present in all his cultures. That sometimes branched forms appear, like those of *B. radiciola*, had been already mentioned by *Beijerinck* in 1889.

The pleomorphism of *B. radicicola*, especially its inclination to grow in branched or in radiate forms, was also well established from the beginning by the publications of *Beijerinck* (1888–1890) and of *Prazmowski* (1890). Unfortunately, the incorrect term "bacteroids" has been widely adopted for this type of growth, though there is not the least doubt that *Brunchorst* and *Frank* were wrong when they assumed that only cell products looking like bacteria, and not real bacteria, were present in the root nodules of the leguminous plants. The radiate growth was considered by *Beijerinck* as indicating relations to the Actinomycetes. *Peklo* (1910) has dwelled upon this point in a paper on "plant actinomycoses." Like *Shibata* (1902), he accepts especially the organisms causing nodules in Alnus and Myrica roots as true actinomycetes. *Bottomley* (1912) and *Spratt* (1912), on the other hand, isolated *B. radicicola* from Alnus, Myrica, and Elaeagnus nodules and see in it the causative agent. This point needs further investigations, which probably will best start again from the experiments carried on by *Hiltner* (1898), who obtained from Alnus nodules thin rods, which grew in an actinomyces-like arrangement. That *B. radicicola* exhibits all marks of the *B. pneumoniae-coli* group can be easily ascertained by comparative studies (*Löhnis*, 1905 *a*) and that all members of this group show branching under suitable conditions, is beyond dispute.[1] In addition, it will become apparent from the further discussion of these points in the following chapters that other characteristics, also accepted by many as necessitating a separate systematic position of the nodule organism, can be generally found with the bacteria as soon as these are made the objects of adequate

[1] Data concerning the branched forms of *B. radicicola* may be found in the publications of *Morck* (1891), *Dawson* (1899), *Hiltner* and *Störmer* (1903), *Süchting* (1904), *Harrison* and *Barlow* (1907), *Rossi* (1907), *Buchanan* (1909), and of *Gage* (1910). That they are erroneously classed as "involution" forms has been discussed on p. 25.

studies. The relations to the vibrios, already indicated by some peculiarities of other members of this group, as mentioned above, are equally discernible with *B. radicicola* and its next kinsman, *B. radiobacter.* It is well beyond doubt that the organism described by *Severin* (1897) as *Vibrio denitrificans* is nothing else than a denitrifying strain of Radiobacter (see *Löhnis,* 1910, p. 486). The characteristic triangular forms found with it, like with all vibrios and spirilla, have been well drawn by *Bordoni-Uffreduzzi* (1888) in his sketch of "Proteus hominis capsulatus" (reproduced as fig. 14 on Plate D). A good survey of the different types of growth of *B. radicicola* has been given by *Conn* (1909) in the drawing reproduced as figure 16 on Plate E (from original fig. 26, p. 99). That the flagellation has been found to be either mono- or peritrichous agrees well with the analogous behavior of other members of this group, as mentioned above.

Bact. rubiacearum, the organism causing nodules in the leaves of tropical Rubiaceae, was found by *Faber* (1912) to resemble *B. radicicola* very closely. Again the branched forms are prevalent in young nodules, and their ability to produce small coccoid bodies, which reproduce the "normal" rods, is the same as in the case of the legume organism. Results obtained by *Georgevitch* (1916) confirm these findings. The causative agent of crown gall, *Bact. tumefaciens,* gives a similar branched growth (*E. F. Smith,* 1911, Vol. II, p. 73).

Among the pigment forming rods some producing a yellow color show distinct relations to the *B. coli* group. *Fr. Levy* (1904) isolated two Coli varieties from flour, of which the first one (*B. coli albido-liquefaciens*) deviated from the type by its inclination to liquefy gelatin, while the other one (*B. coli luteo-liquefaciens*), in addition to this, produced a yellow pigment. While, however, both still possessed the typical fermentative abilities of the Coli group, another strain, isolated from the same source, resembled closely the second one, morphologically as well as physiologically, except that the production of gas was absent. An interesting counterpart to this organism is presented by an old stock culture of *Schroeder's Bact. synxanthum,* studied by *Lehmann* and *Neumann* (1912, p. 392, footnote). Originally a motile yellow short thin rod, producing alkali and staining milk yellow, it was found to be an immotile slime producing organism, Gram-positive in 1899, Gram-negative in 1903, growing like *B. coli* on gelatin, agar, and in milk, which was coagulated; gas was produced from glucose, and only on potato a bright yellow pigment still appeared.

Bact. Fraenkelii, isolated by *Hashimoto* (1899) from milk, is another yellow rod which has been frequently cited as a prominent example of pleomorphism. Growing on agar as small rod with 2–3 polar flagella, it forms in broth long chains of thick immotile globules, looking just like large streptococci. These divide transversely, as well as longitudinally, which leads to "pseudo-ramification." Sarcina-like formations were also seen.

Distinctly Actinomyces-like branching seems to have been observed with yellow rods only twice, i. e., with *B. erythrogenes,* according to *Migula* (1900, Vol. II, p. 458), and with *Bact. solare,* according to a report made by *E. Wolff* (1898). That this occurrence is no reason (contrary to the opinion of the latter author) to remove this organism to the Actinomycetes has been discussed (p. 23). A "Streptothrix polychromogène," described by *Valée* (1903), exhibiting the same rather unique double-pigment production as the first-named species (soluble red, insoluble yellow), perhaps is to be united with *B. erythrogenes.*

Bact. prodigiosum, originally mistaken by *Cohn* for an immotile micrococcus, has been frequently studied with regard to the variability of its pigmentation; its morphology, on the other hand, has been much neglected, though as early as in 1888 *Wasserzug* (1888 *a*) has demonstrated that it, too, can exhibit great differences on various substrates. Besides rods and threads, typical staphylococci, as well as spiral forms, were produced. Large globules (1–2 μ) and yeast-like cells have also been seen. *Slater* (1891) observed with another Prodigiosus variety, which he named *B. corallinum,* that the long threads present in liquid substrates, exhibited a marked tendency to form bud-like projections, which in some instances became so prolonged as to resemble branching. His drawings remind one at once of the branched forms of *B. radicicola* and related organisms. *N. G. Davis* (1901) in the course of studies upon the pigment production of *B. rosaceus metalloides Dowdeswell,* got, after hundreds of replatings, typical cocci

(of 0.5μ diameter) which further remained constant. *Ph. Eisenberg* (1914) says that the morphological alterations exhibited by *B. prodigiosum* are "not conspicuous, usually inconsistent, and not uniform." It seems, however, as if here, like in many other cases, very much attention was spent upon the appearance and disappearance of the red pigment in the cultures and only very little interest was left for microscopical studies.

Bact. violaceum is another instance where *F. Cohn* used a rod for establishing his "genus" Micrococcus (see p. 11). That temporarily globular forms occur also with this organism was probably first mentioned by *Zopf* (1883, p. 68). A related, immotile, slime-producing form, called *Bact. visco-fucatum*, was isolated from butter by *Harrison* and *Barlow* (1905), who found that "elongated branched and cuneate forms were common in old cultures, kept at temperatures below 25° C., and in young cultures at temperatures above 27° C., and in certain special media. These cells were 4–9μ long and up to 0.9μ wide. The cuneate forms were 0.9μ at the larger and 0.3μ at the smaller end. The branched forms were frequently complicated and sometimes tangled together, reminding one of a clumping formation. After the branched forms had become numerous, they broke up by transverse segmentation into short oval elements."

The pleomorphism of the colonies of *Bact. syncyaneum* and of other lophotrichous organisms has been fully studied by *Nyberg* (1912). Thorough experimenting showed that it was possible to induce every one of 140 strains tested to grow either in smooth and round or in wrinkled and branched colonies. Other biological, as well as morphological, differences were correlated with this dimorphism, but they were not made the object of special investigations.

With *B. pyocyaneus* it has been shown by *Guignard* and *Charrin* (1887), a long time ago, that conspicuous alterations in the morphological appearance, as well as in the physiological behavior, can be evoked by slight changes in the substrate (viz., by adding small amounts of antiseptics, like boric acid, phenol, creosote, and thymol). The rods passed over into threads, these into spirilla, which later formed round resting forms, which in their turn were able to reproduce the typical rods. The spiral forms did not produce pyocyanine, but the rods germinating from their resting forms, proved to be normal also in this respect. It is, on the other hand, of course, not very difficult to suppress or alternate the pigment formation more or less permanently also with this organism. *Charrin* and *Roger* (1887) made such experiments with Pyocyaneus, as well as with *B. fluorescens*. As did small quantities of antiseptics, exclusion of air also caused a change from the brilliant bluish green to a light yellowish color. A constantly colorless variety of *B. pyocyaneus* was obtained by *Charrin* and *Phisalix* (1892) by cultivating at 42.5° C. After several transfers the alteration was stable also at lower temperatures, but one passage through the animal reestablished the typical character. A special publication upon pleomorphism and pleobiosis of *B. pyocyaneus* has been contributed by *Schürmayer* (1895). In broth both thick short rods and very thin long threads were observed. *Gamaleia* (1900) noticed that branched forms became frequent with *B. pyocyaneus*, as with other species, by adding lithium compounds to the substrates. *Wassermann* (1903) classes *B. pyocyaneus* among the "pleomorphous schizomycetes," and *Péju* and *Rajat* (1906 *f*) as well as *Wilson* (1907) found that potassium iodide and urea favored the appearance of the different stages of growth also in this case.

Some data upon the different cell forms produced by *B. fluorescens* in the various phases of its life cycle are to be found in *W. Winkler's* (1899) and in *Fuhrmann's* (1906–1908) papers. That all four principal cell forms, viz., small and large cocci, as well as small and large rods may sometimes be encountered in the same microscopical field, was shown in one of the photographs of our second preliminary communication (*Löhnis* and *Smith*, 1916 *b*), reproduced as figure 48 on Plate IV. Curved forms, as well as star-like growth, are equally frequent with this species. The denitrifying Fluorescentes, described by *Christensen* (1903) as "new species," are evidently strains of *Bact. putidum*, exhibiting the same pleomorphism: small cocci and rods (0.5–1.0×0.5–1.5μ) and large cocci, ovals and rods (1.25×1.5–3μ, occasionally up to 4–5μ)

Pseudomonas cerevisiae, whose life cycle was partially investigated by *Fuhrmann* (1906), probably also belongs in the neighborhood of *B. fluorescens*. The same holds true for the

so-called *Bact. bruneum,* i. e. a brown variety of *B. fluorescens,* whose sarcina-like regenerative bodies were photographed by *Matzuschita* (1900), and reproduced as figure 18 on Plate II. An organism first called by *Rullmann* (1897) *Nitrosobacterium,* because of the erroneous assumption that it might participate in the process of nitrification, and later (1898 *b,* 1900) changed by him into a *B. ferrugineus,* is another brown variety of *B. fluorescens,* producing in mineral solutions thin branched threads, often showing terminal inflations; but on agar at 37° C. big "involution" forms were seen to grow up to $1.2 \times 7\mu$.

That the genuine nitrite and nitrate-producing organisms, *Nitrosomonas* and *Nitrobacter,* are also distinctly pleomorphous has been already pointed out by *Winogradsky* (1892), whose attention, however, was especially attracted by the differences distinguishing the "zoogloea" and the motile stages of Nitrosomonas. As the discussion of the true nature of this "zoogloea" will be taken up in Chapter III, the "monas" stage only will be considered here.

Winogradsky was of the opinion that the Russian Nitrosomonas (from Kasan soil) should be accepted, on account of its smaller size, as a species different from the larger Nitrosomonas from Zürich, and also different from the Nitrosomonas from Java, which developed large and small cells at the same time. A comparative study of *Winogradsky's* photographs, however, shows clearly that the Nitrosomonas of Zürich (original fig. 1, reproduced as fig. 49 on Pl. V) has by no means a uniformly large size; small cells are budding forth from and are interspersed between the larger bodies. The Nitrosomonas from Kasan (original fig. 4, reproduced as fig. 50 on Pl. V), on the other hand, displays mostly small forms, but large cells are also present, and their breaking up into small ones by dividing and budding is equally clearly represented. The Nitrosomonas of Java (original fig. 12, reproduced as fig. 51 on Pl. V) evidently takes its place exactly in the middle between both other forms as photographed; here an even mixture of large and small forms is to be seen. *Winogradsky* himself declares the larger cells in this case to be "small colonies of the small forms," a statement which undoubtedly is equally applicable to the Zürich organism. That the morphology of Nitrobacter follows similar lines is to be seen from a comparison of figs. 52 and 53 on Plate V (original figs. 1 on Pl. XVIII, 1891, and 16, 1892). Whether, however, the so-called *Nitrobacter polytrophum* actually represents, as *Beijerinck* (1914 *b*) asserts, a polytrophous modification of the *Nitrobacter oligotrophum,* must be left in doubt. The fact that this new "modification" differed rather radically, morphologically as well as physiologically, from the true Nitrobacter, and that it could not be reverted within 10 years into the original nitrifying form, makes it very probable that some contamination has played its rôle in this as in many other cases, among which the creation of the "Salpeterpilz" by *Stutzer* and *Hartleb* (1897) probably is the best and at the same time the most unfavorably known example. These authors had later (1899 *b,* 1901 *a*) results which agreed fairly well with those of *Winogradsky;* they proposed, however, a new name—"Nitromicrobium" for Nitrobacter—because they noticed the occurrence of budding (visible also in *Winogradsky's* pictures) and thought erroneously that bacteria never show this kind of propagation. Their "Hyphomicrobium" obtained at the same time in their nitrification studies (1899 *a*), which grows either as short motile red, or as thin branched thread, producing round regenerative bodies, and also thought by them to be no bacterium, may have been identical with *Beijerinck's B. oligocarbophilus,* which has been recently removed by its author (1914) into a new genus Actinobacillus, which is closely related to Actinomyces. The colonies are very much alike, especially with regard to the formation of aerial hyphae. Actinobacillus is, according to *Beijerinck* (1914 *b*), devoid of branching, which statement, however, may be justly doubted.

The Actinobacillus found by *Lignères* and *Spitz* (1902) to be the causative agent of the peculiar "Actinobacillose" of South American cattle, also exhibited only coccoid and rodlike cells in the cultures, but the clusters occurring in the pus are made up of richly branched forms, looking like *Metchnikoff's* (1888 *b*) *Pasteuria ramosa.* Th. *Smith* (1918), on the other hand, obtained a pleomorphic bacillus from pneumonic lungs of calves which grew in the tissue only as a fine rod, while in serum cultures flakes with large clubs and also coccoid forms were produced. The author rejects the term Actinobacillus, which he desires to replace by the name *Bacillus actinoides.*

(c) SPORE-FORMING RODS.

Among the early bacteriologists the opinion was rather generally adopted that the spore-forming bacilli do not permanently appear as large rods, but are also able to assume temporarily coccoid shapes. *Perty* (1852), e. g., pictured his *Metallacter bacillus* (on his Pl. XV, fig. 26 *a*) in the manner reproduced in figure 17 on Plate E. *Nägeli* (1877) illustrated his statement, that *F. Cohn* was "fundamentally wrong" in assuming that the bacilli be always long rodlike cells, by a similar drawing, reproduced as figure 18 on Plate E (from original fig. 2). *Buchner* (1882, p. 221) gave another interesting picture, reproduced as figure 19 on Plate E, showing once more that coccoid, as well as rodlike, forms can both be produced by the same organism.

All recent studies have confirmed and amplified these early findings. Many details pertaining to different aerobic species, which were made the object of comparative investigations, may be found in publications by *Gottheil* (1901), *Neide* (1904), *Gruner* and *Fraser* (1912), *Ford* (1916), and others. The large, globular, granular cell forms, described by these authors, are quite similar to those considered to be characteristic of Azotobacter. Their appearance was not stimulated by potassium iodide and urea—i. e., those two substances which *Péju* and *Rajat* (1906) found to be very useful in bringing about analogous changes with several nonspore-forming rods. Branching was observed by *Gottheil* (1901, p. 717), especially with *B. cohaerens*. It takes place, according to *A. Meyer* (1901), earlier than the spore formation, or under conditions which favor the formation of long threads and hinder the production of endospores. That neither the large coccoid nor the branched forms should be classed as "involution forms," has been discussed (on p. 24–27). That motility and flagellation here as in other cases can not be considered to be of fundamental importance for systematic purposes, may be seen, e. g., from a paper by *Ellis* (1906) upon "The Life History of *Bacillus hirsutus.*" *Henrici*, who established this "new species," found it immotile, while it showed to *Ellis* at first polar cilia like a "Pseudomonas," but later the peritrichous flagellation of a "regular" bacillus became visible. An old stock culture of *B. implexus*, described by *Zimmermann* as immotile, assumed motility and so became, according to *Zierler* (1899), a typical *B. subtilis*. *B. mycoides*, on the other hand, when studied by *Lehmann* (1899), refused for a long time to show any motility and most of the rods remained, despite prolonged experimenting, permanently immotile.

Very interesting results with *B. mycoides* have been recorded by *Olsen* (1897), as well as by *Nadson* and *Adamović* (1912). The first-named author noticed that aerobic spore-forming bacilli are much inclined to produce yeast-like forms. When cultivated on wet sand and gravel, *B. mycoides* gave a white dry growth on the surface, which in carefully made preparations showed itself to be made up of frequently branched Actinomyces-like cells, forming short plump "pseudoconidia," which very easily broke off. In the liquid, however, only "normal" rods and threads became visible. Figure 20 on Plate F is a reproduction of figure 14 on Plate V of *Olsen's* publication, illustrating these findings. *Nadson* and *Adamović* (1912) obtained a typical Actinomyces-like growth of *B. mycoides* by adding to broth and agar equal amounts of an old liquefied gelatin culture of *B. mycoides*, which was previously sterilized by being kept 15 minutes at 120° C. Further transfers remained constant; they were unable to produce spores and to dissolve the gelatin.

Some of the forms in *Olsen's* sketch resemble very closely certain types of growth of diphtheroid and tubercle bacilli. It is worth mentioning in this connection that *Niessen* found a Gram-positive diphtheroid "streptobacillus" in syphilitic lesions which is slowly motile, produces typical endospores, shows branching and budding, and appears in small, as well as in large, globular and rod-like forms. The "*Cladothrix stereotropa,*" isolated by *Proca* and *Danila* (1910) from the same source is either identical or closely related to *Niessen's* "streptobacillus." Here again the diphtheroid character is very distinct, yet there are motile rods, too, which form endospores, and also globular immotile, budding cells. A pleomorphic bacillus, obtained by *H. U. Williams* (1912) from a case of tuberculous pericarditis, is another diphtheroid, although spore-forming, evidently belonging to this group. And the same may hold true with regard to *Mycobacillus synovialis*, isolated by *Chantemesse*, *Matruchot* and *Grimberg* (1917), from a case of arthritis. It is a spore-forming bacillus, producing a salmon color in milk and

on potato, much inclined to produce in the cultures branched threads, and therefore accepted by its discoverers as a connecting link between the sporulating bacilli and the actinomycetes.

That *B. anthracis* is not always so constant and monomorphous, as was proclaimed by *R. Koch*, has been shown first by *Buchner* (1882 *a–c*), who succeeded in changing its morphological, as well as physiological, behavior to such an extent that it became very similar to *B. subtilis*. By adding relatively large amounts of sugar, both organisms could be induced to produce distinctly isodiametric cells. *E. Klein* (1883) got similar round forms of 1.3–2.6μ diameter in chain-like arrangement, or sometimes still connected with typical rods and threads, when *B. anthracis* was cultivated in pork broth or pork-broth gelatin, kept at 20–25° C. They either multiplied by dividing into two or four, or by true budding. Their virulence against guinea pigs and rabbits was the same as that of the rods. The latter always reappeared in the animal and could also be obtained from the round cells in artificial culture. The picture given by *E. Klein* (as figs. 1–3 on Pl. XXI) and reproduced as fig. 21 on Plate F, makes it practically certain that, if not all, at least most of these round cells have been microcysts or regenerative bodies. Another drawing, published a few years later (1885) in *Klein's* textbook on pathogenic micro-örganisms and reproduced as figure 22 on Plate F (from original fig. 77, p. 109), also deserves our attention. Here again the character of reproductive organs is fairly well indicated. *Klein* himself places these cells parallel to the "sporangia of nostoc algae." Others of the round cells, however, seem to be of a truly vegetative nature. In a later paper *E. Klein* (1894) reports that he noticed, when studying very early phases of growth of *B. anthracis* "when the colonies are only just visible as angular greyish spots," that the sprouting filaments at the edge were made up of spindle-shaped and oval elements with much vacuolization. His pictures (original figs. 1 and 2 on Pl. I) are reproduced as figure 23 on Plate F. After 4 days only typical straight rods and threads were found.

De Bary (1884, p. 504) saw also anthrax bacilli change into large cocci, but he was unable to secure satisfactory proof of further development. Analogous results were obtained by *Braem* (1889) by keeping anthrax bacilli in distilled water. Good pictures of the different appearance of this species in artificial cultures and under natural conditions were given by *Itzerott* and *Niemann* (1895, original figs. 13–15). They are reproduced on Plate V as figure 54 (from gelatin), figure 55 (from blood, mouse) and figure 56 (from spleen, mouse). All photographs were made with the same magnification (× 1,000), and the smears were all treated in the same manner (stained with methylene blue). *Crookshank* (1896, p. 195) reported that especially from gelatin and glycerin agar "very striking preparations are sometimes obtained with numerous large spherical and lemon-shaped elements." The same facts were described by *Rodet* (1894, p. 18 and 25), as follows:

> À côté de filaments réguliers . . . d'autres présentent des renflements, des dilations et, intercalés aux articles cylindriques, des articles courts et plus ou moins arrondies . . . Articles . . . véritablement sphériques . . . sont alors entremêlés à des éléments moins modifiés et c'est toute une gamme entre les filaments les plus reconnaissables et ces formes singulières qui donnent l'impression de la présence accidentelle d'un microbe étranger.

The round forms which *Matzuschita* (1900) found on salt agar, together with normal spores, are reproduced on Plate V as figure 57 (from original fig. 31). As far as can be judged from sight, they are typical regenerative bodies. Some of them exhibit the budding already observed by *E. Klein*. *Lignières* and *Durrieu* (1902) noticed that a very virulent strain of *B. anthracis* changed on agar within 4 days into long filaments producing round buds or assuming irregular spiral shape, while on potato a yellowish growth appeared, made up of pear- and club-shaped cells. Some other interesting proof of the pleomorphism of *B. anthracis* was secured by *Mme. Henri* (1914) by treating a watery suspension of the bacilli with ultraviolet rays. Most of the cells were either killed or remained normal; but some of them gave colonies of such forms as are reproduced on Plate V in figure 58 (from original fig. 4), which are very similar to those seen by *E. Klein* and *Matzuschita*. That they were regenerative bodies was proved in this case by their reverting back to normal rods. Sometimes, however, *Henri's* experiments led to a stabilizing of the spherical growth. The typically coccoid cells reproduced in figures 59 and 60

on Plate V (from original figs. 5 and 6) did not go back to the rod form. Moreover, an actinomyces-like growth developed, made up of branched, Gram-negative, nonsporulating filaments, shown in figures 61 and 62 on Plate VI (from original figs. 7 and 8), which resemble very much the atypical growth of *B. mycoides,* obtained by *Nadson* and *Adamović.* These filaments did also not revert to the rod form directly, but only after having formed again the coccoid regenerative bodies, reproduced in figure 63 on Plate VI (from original fig. 9), which process agrees closely with the behavior exhibited by *B. azotobacter* and other organisms tested in our own experiments (1916), when passing over from one subcycle into another.

With *B. subtilis* similar round forms were studied by *Buchner* (1882) and by *E. Klein* (1885, p. 110). The photographs of *B. subtilis* reproduced as figures 64 and 65 on Plate VI from our preliminary papers (*Löhnis* and *Smith,* 1916 *a,* fig. 26; 1916 *b,* fig. 6) make interesting counterparts to those of *B. anthracis,* as well as to the well-known pictures of "bacteroids" of *B. radicicola.* Distinctly filamentous growth, resembling Actinomyces, has also been obtained.

An old stock culture of the so-called *Tyrothrix tenuis,* originally isolated by *Duclaux,* gave us (1916 *a*) very similar results as did *B. subtilis. W. Winkler* (1895), who tested several of *Duclaux's* "Tyrothrix" cultures, speaks also of broad "involution" forms, which probably have been of the same nature, as far as can be judged from his paper and from his drawings. Analogous findings were recorded by *Viehoever* (1913, p. 230) in regard to *B. Pasteurii.* The globular forms produced by segmentation of the rods, which he calls "micro-oidia," probably are to be classed as regenerative bodies like those obtained by *Henri* with *B. anthracis.* That the yeast-like "involution" forms, considered by *Miquel* and *Cambier* (1902, p. 633) as characteristic of *Urobacillus Maddoxii,* are actually not of such a distinctive value as these authors thought, needs no special discussion.

A bacillus isolated by *Pansini* (1890) from sputum and described as "No. 6" is another example of pronounced pleomorphism within the Subtilis-Mesentericus group. Small cocci, large yeast-like cells, and rods of different size have been recorded. With other bacilli from the same source "coccoid degeneration forms" were also registered by this author.

A bacillus found by *Maassen* (1904) in "Hackfleisch" gave branching under the influence of lithium salts added to the substrate. Figure 66 on Plate VI is a reproduction of the original figure 11 on Plate XIV. Practically the same development was shown by another not completely studied "yellow bacillus No. 41" from soil, used in our preliminary experiments on the life cycles of the bacteria (1916 *a*), in this case, however, without being stimulated by lithium or any other specific stimulant.

Gamaleia (1911, p. 211) found lithium salts equally useful for producing branched growth of *B. Megaterium.* The normal rods of this species, originally described by *De Bary* (1884, p. 500) as being 2.5μ broad, showed only a width of 0.6–0.8μ when reinvestigated by *Lehmann* and *Neumann* (1912, p. 461). It is to be expected that here again small and large cell forms may become visible, according to the subcycles entered by the organism in the course of its development. Long chains of big spherical cells have been also recorded by *De Bary* (1884, p. 503) for *B. Megaterium,* and it has been mentioned (p. 41) that the presence of a small bacterium was found to be distinctly favorable for inducing this transformation, just as was the case when *B. radiobacter* was growing together with *B. oxalaticus* or with a stable rod-like strain of *B. Azotobacter. Bac. danicus,* found by *Löhnis* and *Westermann* (1908) to be a common symbiont accompanying *B. radicicola* in the root-nodules of leguminous plants, seems to be influenced by the latter in an analogous manner. As with *B. Megaterium* and *Azotobacter* the reduction of size in pure cultures has been also noted in the case of *B. oxalaticus. Migula* (1900, Vol. II, p. 538) found that at first the rods measured $2\frac{1}{2}$–3×4–8μ; later, however, not more than $1.2 \times 1.8\mu$.

B. malabarensis, isolated by *Löhnis* and *Pillai* (1907) from East Indian soil, is of great morphological interest, not only because it is even more inclined than the species mentioned to assume distinctly Azotobacter-like forms, but also because of its liability to produce peculiarly looking beet-shaped, spermatozoon-like, and later long-tailed spindle-shaped cells, as are shown

in figures 67 on Plate VI and 266 on Plate XXI. These forms present a remarkable counterpart to the appearance of Rhabdochromatium, just as the large Azotobacter-like cells resemble those of Chromatium. Probably the natural relationship of these little known sulphur bacteria will be better understood, after the life history of the large spore-forming bacilli has been more completely studied. *Migula's* remark (1904, p. 31) that no such cell forms are to be found with typical bacteria can not be accepted as correct. And that the peculiar, swollen, and tailed cells can not be discarded as "involution" forms, is proven by the fact that they, too, precede the formation of spores. *Duclaux* (1883, p. 654) described this a long time ago, referring to the analogous behavior of his *Tyrothrix virgula*, with the following words:

> Ce renflement grossit pendant que la portion du bâtonnet qu'il n'a pas atteinte se résorbe et s'amincit de plus en plus, de sorte que l'être tout entier prend des formes très singulières . . . Quelques-uns d'entre eux rappellent d'une manière frappante des spermatozoïdes. C'est dans les renflements que se fait ensuite le travail de formation des spores.

Bac. Baccarinii, isolated by *Macchiatti* (1898) as a causative agent of the "mal nero" of the grapevine, is another example of distinct pleomorphism among the spore-forming bacilli. From typical cocci up to long threads practically all forms were seen.

Bac. tumescens shows the same character, as was first pictured by *Zopf* (1883, p. 66) in the drawing reproduced as figure 24 on Plate G (from original fig. 23), and later studied anew by *A. Koch* (1888) and by *Garbowski* (1907). The last-named author made at the same time a fairly complete study of *Bac. luteus sporogenes Wood* et *Baker*, which led to many confirmative results. Good branching has been recorded in this case, as well as the formation of those small coccus forms (of only 0.8–1μ diameter), which simulate very much streptococci and sarcinae, and which have been described as "micro-oidia" by *Bredemann* (1909) for *B. Amylobacter*, and by *Viehoever* (1913) for *B. Pasteurii.*

That all the different species or varieties of the Azotobacter group are probably types of growth of spore-forming bacilli, is indicated by the results of our more recent investigations (*Löhnis* and *Hanzawa*, 1914, L. and *Smith*, 1916). Several of the photographs accompanying our 1914 paper present interesting counterparts to those published by *Henri* at the same time for *B. anthracis*. Especially the small round Azotobacter cells (regenerative bodies) reproduced as figure 68 on Plate VI (from original fig. 28) look very much like *Henri's* Anthrax cells in figures 59 and 60 on Plate V. Figure 69 on Plate VI (reproduced from *Löhnis* and *Smith* 1916 *a*, fig. 20) demonstrates, in addition, that it is possible to induce a strain, which originally showed the typical character of Azotob. chroococcum, to grow in a manner very much resembling that of the normal *B. anthracis*. Fig. 70 (reproduced from *Löhnis* and *Smith* 1916 *a*, fig. 16), on the other hand, represents an interesting intermediate stage in the development of small rods, in which case *B. azotobacter* assumes forms very similar to *B. radiobacter* and other organisms belonging to the *B. pneumoniae* group. A comparison of fig. 70 with figs. 38 and 39 on Plate IV, illustrating the analogous stage in the life cycle of *B. pneumoniae*, will further prove this fact. (The clusters visible in fig. 70 are the outgrowths from the symplasm, to which reference will have to be made in Chapter III.) Figures 71 and 72, taken from a paper by *Walton* (1915, original figs. 1, 9 and 10) show the small short rod-like forms from a one day old culture, and the typical large Azotobacter cells from the same culture after 7 days growth. Most of the strains studied by this author underwent an analogous change regularly, though in other cases the small forms have proved themselves to be much more persistent. The pleomorphism of *B. azotobacter* was already noticed to some extent by *Beijerinck* (1901 *b*). More data were furnished by *Düggeli* (1905 *a*), *H. Fischer* (1905), *Löhnis* and *Westermann* (1908) and by *Krzemieniewski* (1908). Branched forms were first seen by *H. Fischer* and by *Löhnis* and *Westermann;* but they were considered by the first-named author to be "involution" forms. *Peklo* (1910) supposed that as *B. radicicola* and spore-forming bacilli, so also Azotobacter be related to the Actinomycetes. Of special importance are *Prazmowski's* (1912) extended investigations upon morphology, cytology, and physiology of the Azotobacter group, which were further confirmed and amplified by the studies made by *Löhnis* with *Hanzawa* (1914) and with *Smith* (1916).

Our first preliminary report upon the life cycles of the bacteria (1916 *a*) contains the description and pictures of most of the various types of growth of *B. azotobacter*. A schematic sketch of the complete life cycle of this organism was reproduced from the last-named paper as figure 1 on Plate A; and on page 36 two tables were reprinted, showing that essentially the same complex morphology was not only observed with all Azotobacter strains tested, but that it could also be traced in all other groups of the bacteria.

Harrison (1900) has described variations in size and shape, as well as the appearance of Y forms, with *B. alvei*. Like other species connecting aerobic and anaerobic spore-forming bacilli, it seems to be much inclined to lose its ability to form spores, as was noticed by *Lehmann* and *Neumann* (1912, p. 505).

Pleomorphism and pleobiosis of the more or less strictly anaerobic bacilli have been firmly established, especially by the investigations of *Grassberger* and *Schattenfroh* (1900–1907) and by *Bredemann* (1909). It remains to be seen, however, whether or not the study of the complete life cycles of these organisms will support the standpoint taken by the latter author, who is of the opinion that a considerable number of anaerobic species, mentioned in the literature, should be cancelled and united with *B. amylobacter*. That as with aerobic, so also with anaerobic spore-forming bacilli the morphological changes can not be stimulated in the same manner as with various nonspore-forming bacteria, i. e., by adding potassium iodide and urea, was reported by *Péju* and *Rajat* (1906 *e*). Change in motility and cell form of *B. amylobacter* has already been seen by *Van Tieghem* (1884, p. 110). Besides rod-like forms, "cellules sphériques et ovoides" and others "enroulées en helice" were mentioned, all of which were found to be able to produce spores. Analogous results have been recorded by *Prażmowski* (1880) for his Clostridium butyricum and Polymyxa. His drawings, reproduced as fig. 25 on Plate G (from original figs. 1, 2, 6, and 7 on Pl. II), illustrate that he saw changes between "Clostridium" and "Plectridium" type, formation of curved, coccoid, and large inflated cells and in the accompanying text it was especially pointed out that the last-named form became visible when the development of luxuriantly growing cultures was at its height, so that they should not be classed as "involution" forms. They were seen to return to the normal rod form by segmentation. Spherical cells were observed by *Prażmowski* only with his Clostridium Polymyxa, but it was, indeed, quite probable, as *Zopf* (1883, p. 70) presumed, that they would also be discovered with Clostridium butyricum. As mentioned above, *Van Tieghem* has seen them, and in figure 26 on Plate G drawings from *Bredemann's* paper on *B. amylobacter* (1909) have been reproduced, showing the forms called by him "micro-oidia." They were found with all of his strains and under quite suitable conditions, but he was unable to revert them into the typical rod-like anaerobic growth. On aerobic plates they gave small soft punctiform colonies.

The results obtained by *Winogradsky* (1902) with his Clostridium Pasteurianum are very similar, and *Bredemann* includes this "species" among the varieties of *B. amylobacter*. As figure 73 on Plate VII one of *Winogradsky's* photographs (original fig. 3) has been reproduced, showing large and small coccoid forms, curved cells and apparently also some branching and budding. The morphological, as well as physiological, variability was found to be so great with this species that the different strains were hardly recognizable as being of the same kind.

The behavior of and the relationship existing between the various anaerobic butyric acid, pathogenic, and putrefying bacilli have been fairly well elucidated by the investigations of *Schattenfroh* and *Grassberger* (1900), of *Grassberger* (1902–1905), and of *Grassberger* and *Schattenfroh* (1907). Motility and cell form, but also appearance of colonies and physiological character, exhibit very wide variabilities. Some strains are comparatively stable, while others are easily "denatured," which expression is used by the authors for those cultures which have lost, temporarily or permanently, their motility and their faculty to form spores. As among the latter sometimes the production of gas also ceases entirely, and the butyric acid is largely replaced by lactic acid, the general character of such strains becomes very similar to that of certain lactobacilli. As I have pointed out (1910, p. 200) this transformation deserves to be investigated more thoroughly. *Laxa* (1911) found that treatment with formaldehyde was very

efficient in bringing about such alterations, not only with butyric acid, but also with putrefying strains. Presence of sugar favors the production of swollen forms and stimulates the fixation of nitrogen in the same manner as it does with aerobic spore-forming bacilli, while substrates rich in albuminous substances increase the tendency to pass over into the putrefying plectridium type (*B. putrificus*).

B. putrificus, *B. oedematis maligni*, as well as *B. Chauvoei*, may all be, according to *Grassberger* and *Schattenfroh* (1907) and *Bredemann* (1909), merely adaptations of *B. amylobacter*. The results thus far collected make a thorough study of the complete life cycles of these organisms very desirable and promising.

Coccoid, lemon-, and club-shaped forms of the organism of symptomatic anthrax were observed in cultures by *Ehlers* as early as in 1884. His work was discredited by *Kitt* (1887), but later confirmed by *Grassberger* and *Schattenfroh* (1907). *Fraenkel* and *Pfeiffer* (1895), as well as *Piani* and *Galli-Valerio* (1895), dwelled upon the pleomorphism shown by this species in the tissue, where small and large rods, dumb-bell shaped and coccoid cells were found. As figure 27 on Plate H drawings of *Ghon* and *Sachs* (1903, original figs. 13, 14, 16–18) are reproduced to illustrate this point. Except the cells shown at the left side, which were taken from the muscle of a pigeon, all forms were grown on the agar plate. The small branched cells resemble certain lacobacilli very much. Two of *Grassberger's* (1903) photographs, reproduced on Plate VII as figures 74 and 75, may complete the picture. Figure 74 (from original fig. 54) gives an analogous mixture of small and large rods, as was shown in figure 69 for one of our spore-forming Azotobacter strains. And figure 75 (from original fig. 21, material taken from sugar broth) could be easily mistaken for a photograph of a typical Azotobacter culture. This parallelism is enhanced by the variability in motility, the instability of spore formation, by the shape of the colonies, and especially by the possibility, proved by *Grassberger* (1905), to adapt *B. chauvoei* to aerobic life with loss of pathogenicity. Several objections have been raised by *Hibler* (1908) against the work done and the standpoint taken by *Grassberger* and *Schattenfroh*. His own work, however, seems to be much more open to criticism. On Plate VII, as figures 76 and 77, two photographs of symptomatic anthrax are reproduced from his book, where they appear widely separated (on Pl. X, fig. 16, and Pl. XVI, fig. 7). Both show the characteristic big round cells accompanying the rods. But only in the first case *Hibler* is inclined to admit this pleomorphism, because here the material was taken from a pure culture. In the second case, representing the analogous development in the peritoneum of a mouse, he does not hesitate to state: "Die verschieden grossen dunklen kugligen Körper sind Granula aus aufgelösten Mastzellen, der unterste Phagozyt schliesst auch zwei solche Körner ein," though, of course, this statement remains entirely without proof, and the obvious likeness of the two photographs (despite the different, not exactly defined magnification) creates considerable doubt whether *Hibler's* standpoint was not too strongly influenced by the monomorphistic doctrine with its well-known simple (but unfounded) "explanations."

A good example of true branching of the oedema bacillus has been given by *Grassberger* (1903) in the photograph reproduced as figure 78 on Plate VII (from original fig. 42). The material used was taken from sugar agar. *Ghon* and *Mucha* (1905) isolated a closely related organism from a case of peritonitis, which in the peritoneal exudate first looked very much like *B. coli*. In sugar agar it proved to be highly pleomorphous. Besides the more normal cells, club-shaped, curved vibrio-like rods became visible, "und in grosser Menge Gebilde in den verschiedensten Grössen und Formen, die vielfach kaum noch als Bakterienformen angesprochen werden konnten." Branching was frequent in hydrocele fluid.

With *B. tetani*, *Kanthack* (1896) and *Kanthack* and *Connell* (1897) have seen branchings, especially in young cultures (18–24 hours old), while in old cultures these forms usually disappeared. Clubbed cells and mycelial growth also were recorded by the last-named authors. *Tavel* (1898) photographed budding and branching of a pseudo-tetanus bacillus from the intestine, but did not mention this fact in his paper. *Hibler* (1908) noticed that the characteristic drum-stick form of *B. tetani* became regularly visible in cultures several days old, while with younger material the spores were very often located in the middle of the rods, which not

infrequently looked like clostridia. Substrates rich in carbohydrates produced such abnormal forms exclusively. Even in old cultures no plectridia appeared under such conditions.

The anaerobic Vibrio Rugula, whose spore formation has been closely studied by *Prazmowski* (1880) was placed by *Lehmann* and *Neumann* (1912, p. 156, footnote) in the neighborhood of *B. oedematis maligni.* In fact, it seems certain that this organism has nothing to do with the genus Vibrio, as it is accepted in the modern literature. *Dujardin* (1841, p. 218) placed it close to his *Vibrio* (now *Bacillus*) *subtilis,* and he pointed out already, that Vibrio Rugula grows either curved or straight, occasionally forming "fils alternativement droits ou flexueux." *Prazmowski's* drawings are reproduced as figure 28 on Plate H (from original figs. 10 and 11 on Pl. I). As this organism was able to decompose cellulose, and *Omelianski's* photographs of his anaerobic cellulose bacilli show the same curved cells with terminal spores, it seems correct to assume that this is the proper classification of "Vibrio Rugula."

(d) SPIRILLA AND SPIROCHAETS.

The question has not been definitely settled whether the spirochaets are to be considered to be true bacteria, or whether they should better have their place between bacteria and protozoa, or perhaps among the latter themselves. Morphological, cytological, as well as physiological, reasons have been submitted in favor of the latter view. *Prowazek* (1907*a*) mentions in this respect especially the ribbon-like structure, the undulating membrane, the longitudinal division and the sexual differentiation, which, as well as the cysts, in his opinion are never to be found with bacteria. *Keysselitz* (1907) adds that also the flexibility of the spirochaets should be accepted as a proof of their protozoal nature, because he considers bacteria to be always of a rigid structure. *Hölling* (1911) and *Klimenko* (1914) point to cytological reasons in favor of the protozoa theory. *Krzysztalowicz* and *Siedlecki* (1908), as well as *McDonagh* (1912–13), furnished many details concerning sexuality and reproduction, which would support this view. *Carpano* (1914) even believes the rosette-like arrangement, sometimes displayed by spirochaets, to be valid proof of their protozoal nature. *Novy* and *Knapp* (1906), on the other hand, emphasized that on account of their flagellation, transverse division, and other marks the spirochaets should be united with the bacteria. *Zettnow* (1906) took also his stand against the assumed longitudinal division, and he thought, in addition, to have obtained proof of peritrichous flagellation. This, however, was refuted by *Keysselitz* (1907), *Schellack* (1907–09) and *Fantham* (1908) as being an error, caused by a separation of the fibrils in the undulating membrane; but *Schellack* (1909), as well as *Dobell* (1912) and *Swellengrebel* (1912), have shown that the cytology of these organisms is the same as that of bacteria. Transverse division and other reasons are mentioned by the two last-named authors in favor of their opinion that the spirochaets should be placed as a special group among the bacteria. The studies of *Gross* (1912) and of *Meirowsky* (1914*b*) upon their modes of reproduction equally support this view. In addition, *Meirowsky* (1914*a*) has pointed out that the true branching found by him with all spirochaets tested, should be accepted as strict proof of their bacterial nature. It goes without saying, that he was mistaken in this direction. Nevertheless, it seems that an unbiased consideration of all items concerned, including especially the reproductive processes to be discussed in Chapters II–IV, will support the view that the spirochaets, or at least a part of them, show much more the general character of the bacteria than that of the protozoa. Some organisms now included in this group might perhaps be better separated and brought into closer connection with the protozoa. At present, however, where their life history is hardly much better known than that of the bacteria related with them, it seems more useful to take advantage of all the results collected so far, and especially of those which might be helpful in further investigations upon the life cycles of their bacterial kinsmen, the vibrios and spirilla.

Vibrio cholerae, though at first also declared by *R. Koch* and his pupils to be strictly monomorphous and absolutely constant in its activity as in its appearance, can now be considered to be one of the best known examples of a wide pleomorphism. It is very much inclined to assume all the form types of the old form genera of *F. Cohn.* As early as in 1885 its ability to

grow in globular shape was discovered by *E. Klein* (1885*a*). He found that at room temperature, but not at 38° C., after several days the curved bacilli pass over into circular forms, which later split up lengthwise into two regular comma bacilli. *Ferrán* (1885) had analogous results in diluted broth (*Koch's* broth is declared by him to be too concentrated). He calls these round forms "oogones," and reports that observations in the hanging drop also revealed the presence of smaller round bodies which, as "pollinodes," fertilized the oogones. Later the oospores are said to have liberated granules in large numbers, which in their turn grew up to "corps muriformes," and that these have reproduced some long fine spirilla, which later subdivided themselves to typical vibrios. *Ermengem* (1885), who quoted these findings extensively, was only able to confirm the report of the Spanish author as far as the granules and the "corps muriformes" were concerned, and when one reads *Ferrán's* original report, wherein he comes to the conclusion that the cholera vibrio is a type of growth of a "Peronospora Barcinonae," it appears, indeed, by no means surprising that this work could not gain any acknowledgment among careful bacteriologists at that time. Yet, in the light of many other facts discovered more recently, and after separating facts from theories, it becomes very probable that *Ferrán* has seen nearly all of the complete life cycle of this organism. The data to be given in the next chapters upon gonidia, gonidangia, regenerative bodies, symplasm and conjunction, will elucidate and confirm many of his findings. That *Ferrán* also saw long fusiform threads containing granules in old cultures, and that he found it difficult to revert these straight forms to the normal curved rods, is another point of interest. Moreover, it should be mentioned that *Ferrán*, according to his report, was able to find all the different forms not only in his cultures, but also in the feces of diseased persons, as well as in the exudates from inoculated animals. *Babes* made also some observations upon morphological changes and on differences in the appearance of the colonies of the cholera organism as early as in 1885. *Klebs*, too, wrote in 1887 (p. 359): "in sehr zahlreichen Fällen enthält der Choleradarm nicht die characteristischen Kommaformen, sondern Modificationen derselben," and he mentions as such especially ovoid cocci and large globules.

Papers by *Dowdeswell* (1889–1890), as well as by *Schroen* (1891), have brought much confirmation to the discoveries of *E. Klein* and *Ferrán*. However, they also met the same fate, though the observations recorded therein were based on continuous microscopic observation of the living organisms on the warm stage. In addition to the forms mentioned, *Dowdeswell* described and made drawings of branched filaments and of large triangular cells, which only recently have been rediscovered and photographed. *Metchnikoff* (1894) got large dumb-bell shapes, showing lateral buds and branches, very similar to those which he first noticed with the bacilli of avian tuberculosis, when he grew the cholera vibrio in symbiosis with a white coccus. Cells looking very much like Actinomyces, small ovals, cocci, short straight rods, and spermatozoid-shaped bodies have also been seen by him, and the cholera organism was therefore classed as an "example frappant du pléomorphisme si répandu dans le monde des bactéries." *Gruber* (1894) pointed out that some strains differ widely from the typical cholera vibrio, either by their pointed ends, or by assuming the shape of nearly straight rods possessing 4–6 long polar flagella. Motility, appearance of the colonies, nitroso-indol reaction, as well as the behavior in the animal test, were all found to be more or less variable. *Gruber* pays also special attention to the "Vibrio Ivanoff" which at first was declared by *R. Koch* to be a genuine cholera vibrio; later, however, an "entirely different species." In their "Atlas" *Fraenkel* and *Pfeiffer* (1895) published a good picture of various forms studied by the authors mentioned above, which to them, however, are merely "involution" forms, because they came from a broth culture three weeks old. Their photograph (original fig. 99 on Pl. XLVIII) has been reproduced as figure 79 on Plate VII; the "crippled involution forms" stain well, while the "typical" vibrios are pale and dissolving. As figure 80 a reproduction from *Itzerott* and *Niemann's* "Atlas" (1895, Pl. IX, fig. 53) has been added, showing again what these authors term "involution" forms, though the very characteristic appearance and the great similarity of the cells visible in both pictures are certainly not in agreement with the assumed "degeneration."

Cunningham (1897) emphasized that "many vibrionic organisms under certain circumstances have the power of multiplying indefinitely in the form of cocci, diplococci, and short straight rods, although under other conditions they are capable of assuming typically vibrionic characters." And he adds: "This is a fact which is well known to everyone who has practically studied the subject." *Gamaleia* (1900, p. 207) obtained giant spirilla and globules within 24 hours, when he grew the cholera cultures in broth containing ½–1 or on agar with 1–2 per cent lithium chloride. *Nakanishi* (1901) noticed that the globules of *V. cholerae* and *Metchnikovii*, whose diameter was about four times as large as the width of a vibrio, reverted readily to the typical comma form, even if they were taken from cultures 15 weeks old. *Kohlbrugge* (1901*a*) got long branched filaments of the cholera organism in blood serum, which he (erroneously) described as "Cladothrix-like." By repeated inoculation into animals *Shibayama* (1902) even succeeded in developing strains producing constantly thin branching filaments, which, however, were quite avirulent. Most of the important results recorded by *Almquist* (1904–1917) will have to be discussed in Chapter II, as referring to reproductive organs and processes. His cultures gave also small and large coccoid forms, straight rods which morphologically resembled the typhoid organism, and much budding. One culture, mentioned in his 1916 paper, grew during two years constantly in coccoid shape, though still exhibiting the normal behavior in the agglutination test. *Maassen's* (1904) work contains interesting details concerning the stimulating effect of various salts in bringing about the morphological changes in the cholera vibrio, which to the author are merely "pathologic deformities." *Péju* and *Rajat* (1906*e*) found that 5 drops of their potassium iodide solution added to the cholera culture produced coccobacilli, while 8–9 drops gave long threads. *Hammerl* (1906) discovered spherical bodies of 1–6μ diameter and branched cells in many cases. They were present already, and sometimes exclusively, in young cultures; they could be transferred for weeks and months, and their motility was very pronounced. The author, therefore, correctly refutes the "involution" theory. *Horowitz* (1911) not only observed the same pleomorphism as recorded by the earlier authors, he reports also upon a very great variability of the agglutinability of his strains, which experiments, however, can not be accepted as conclusive. *Lehmann* and *Neumann* (1912, p. 513) say concerning the "atypical" forms of *V. cholerae:*

> Unter besonders günstigen Bedingungen . . . trifft man . . . vorwiegend kurzovale, kokkenartige Gebilde. . . . In salzarmen, besonders aber auch in sehr salzreichen Flüssigkeiten bilden manche Cholerastämme auffallend geblähte bis kuglige Formen, die vollkommen fortpflanzungsfähig sind. . . . Wir haben auch manchmal lange, schöne Fäden gefunden, die von Fluorescens nicht zu unterscheiden waren, in den nächsten Culturen aber wieder nur als lange dünne Stäbchen auftraten. Wirklich gekrümmte Formen waren selten. Dies Spiel zeigt sich bei einer echten Kultur aus Hamburg von 1892 stammend nun schon seit über 10 Jahren.

The most complete survey of the different types of growth exhibited by *V. cholerae* has been given by *Stamm* (1914). Some of his photographs are reproduced as figures 81–83 on Plate VII (from original figs. 2, 4, 5, and 15 on Pls. XI and XII, and figs. 1 and 2 from the text, p. 512 and 524). He cultivated 13 strains under comparatively natural conditions, viz., in water; 6 of them remained constant, while 7 changed in their morphological as well as in their physiological behavior to a considerable extent. They all lost their agglutinability, and they did not return to the original type within 30 months, if frequently transferred. Inoculations from old cultures, however, gave again curved forms. The cocci, though themselves not agglutinable, produced a rabbit serum which agglutinated the typical *V. cholerae.* 37 strains, isolated by *Popoff-Tscherkasky* (1914) during the Balkan war, and kept for 4–9 months without being transplanted, grew after the first reinoculation as a mixture of cocci, short rods, and vibrios. The next transfer on agar gave after 24 hours at 37° C. very large irregular threads, big globules, and large rods, but not a single vibrio. These forms replated on agar gave only colonies containing vibrios of somewhat larger size, which then again proved to be stable. That the appearance and disappearance of the different forms is the result of the various phases of the life cycle of the cholera organism has been ascertained by *Olsson* (1915) under *Almquist's* direction. Atypical wrinkled colonies always gave him immotile cells, but these could be changed back into the motile form producing the typical colony.

How the strictly monomorphistic view, as established by *R. Koch,* in regard to his "Komma Bacillus," has changed within the last 30 years, even among his collaborators and followers, may be seen from the following quotations: In 1892 *Friedrich* in volume 8 of the "Arbeiten aus dem Kaiserlichen Gesundheits-Amte" tried to deal effectively with all that had been discovered by authors like *Dowdeswell, Cunningham,* and others. As far as this was not in accordance with the "legitimate" findings of *R. Koch* and his pupils it was easily "explained" as plasmolysis, vacuolisation, granular decomposition, degeneration, or simply fiction. *Dowdeswell's* "claims" were "not to be taken seriously." Nevertheless, some alterations in the appearance of the colonies and cells, as well as in the pigment production, are admitted, though on account of their instability they were not accepted as true variation. In 1903 *Kolle* and *Kolle* and *Gotschlich* admitted that the morphological marks, except the "legitimate" polar flagellum, can not be considered specific. The same was declared to be true in regard to the colonies on the gelatine plate, which were mostly found to be dimorphous. Only the agglutination test was strictly upheld, and those cases discarded as not being cholera, where a quickly fatal disease, showing the symptoms of cholera, was caused by vibrios which were not agglutinated by the true cholera serum. In 1912 *Baerthlein* furnished another contribution in volume 40 of the "Arbeiten aus dem Kaiserlichen Gesundheits-Amte" wherein now, however, the "mutation" of *V. cholerae* and of other bacteria was discussed extensively. Three types of colonies made up by different cell types were found and also traces of a cyclic development were discovered. Additional data upon this subject were published by *Feldmann* (1917) and by *Baerthlein* (1918).

As was mentioned on page 56, *Pollak* (1913) obtained colonies and cells looking like those of *V. cholerae,* when cultivating *B. faecalis alcaligenes* on the blood agar recommended by *Dieudonné* for cholera diagnosis.

The life cycle of the vibrio isolated by *Finkler* and *Prior* (1884) from cases of cholera nostras, which was named by *Buchner* on account of its pleomorphism *V. proteus,* received a fairly complete description by its discoverers already in 1885. Their very interesting, although frequently doubted, observations upon the reproductive processes will be quoted in Chapters II and III. The curved form was found to occur only temporarily. It was soon replaced by big globules, thin and thick rods, club-shaped cells, and other forms very similar to those observed much later also with *V. cholerae.* The ends of the curved cells were either rounded or pointed, sometimes their appearance was different at the same cell. *R. Koch* (1884 *b*) defended the "strictly specific" nature of his "Komma Bacillus" strongly against *Finkler* and *Prior,* whose findings were discredited as being the result of experiments with impure cultures. The last-named authors, however, could point out in return that *Koch's* own slides exhibited also a much greater pleomorphism of the cholera organism than this author was willing to admit. *Ermengem* (1885), too, did not hesitate to take his stand against *Finkler* and *Prior,* because differences in the appearance of the colonies and the cell form were to him full proof of "impurities." *Firtsch* (1888), on the other hand, showed soon that unquestionably pure cultures of the Finkler-Prior vibrio are able to produce four clearly different colonies, which, if found alone, undoubtedly would be considered to be those of four different species. Motile and immotile comma forms, spirals, straight rods, spindle-shaped, ovoid, and monad forms were again present, and *Firtsch* succeeded in many cases to change experimentally the various types of cells and colonies into each other. That his observations and conclusions were correct has been proven more than 25 years later by *Fürst* (1914), who with single-cell cultures secured analogous results. The different cell forms remained so constant, when frequently transferred to fresh substrates (after 5–6 days), according to standardized laboratory rules, that they could be easily mistaken for different species. When kept for 2½ months and then reinoculated many of them reverted to the original vibrio type. And 4-months' old cultures gave 100 per cent normal cultures.

Bonhoff (1896) isolated an organism from cholera nostras which first appeared very much like *B. coli,* macro- as well as microscopically. Later, however, it assumed comma, S and screw forms, while other cells presented themselves as diplococci. The rods possessed two polar flagella, representing an interesting connecting link between Vibrio and Pseudomonas.

E. Klein (1905) met in Cardium edule a pathogenic "Vibrio cardii," which he places between *V. cholerae* and *V. Finkler-Prior*. On agar, gelatin, and serum it forms abundantly convex and globular cells, which retain their motility and propagative ability, and they are declared to be very similar to those found before by the same author in cases of true cholera.

Kohlbrugge (1900) described a "new" vibrio from water under the (preoccupied) name *V. proteus*, which grew on agar as a short rod, in gelatin and broth as a vibrio, and in water as a coccus. Tested later (*Kohlbrugge*, 1901 *a*) on blood serum, it produced long branched threads as did *V. cholerae*. Another pleomorphous vibrio from water was described by *Jorge* (1896), again resembling *B. coli* in several respects and apparently still more closely related to *V. denitrificans Severin*, whose character and systematic position was discussed on page 59. *Jorge's* organism grew on agar mostly as a straight rod, in broth very much like *B. coli*, while on gelatin distinctly curved forms up to long spirals were predominant, some of them showing inflations at their ends. The pathogenic fluorescent vibrios, isolated from water by *Fuhrmann* (1905), may also be looked upon as indicative of relations connecting this group and that of *B.* (*Pseudomonas*) *fluorescens*.

Vibrio phosphorescens Dunbar gave, when cultivated by *Maassen* (1904) on agar containing 2–3 per cent lithium chloride, branched cells in very great numbers. As figure 84 on Plate VII *Maassen's* two photographs are reproduced (from original figs. XIII, 10 and XIV, 3). The forms shown are very similar to some drawn by *Dowdeswell* in his investigations upon cholera, mentioned above.

Several of the highly pleomorphous marine Hali- and Photobacteria described by *B. Fischer* (1894) should very probably take their place here. This is especially true concerning his *Halibacterium polymorphum*, which gave practically all kinds of cell forms, and all these in different sizes, in cultures not older than 2–3 days, and on most suitable substrates. There were recorded (l. c., p. 36): globules, short rods, comma and screw forms, irregular cells of large size (sometimes larger than yeast cells), pear-, hook-, and club-shaped forms, very long spindles with pointed ends, and irregularly curved threads. *Halibacterium pellucidum* and *Photobacterium tuberosum* exhibited also much of the characteristics of a vibrio. It is the same with *Photobacterium balticum* according to the description furnished by *Barnard* (1899).

Weibel (1887–1888) isolated several *Vibriones saprophiles*, another from the mucus of the nose, and one from the tongue, all of which exhibited pleomorphous tendencies. The "*Vibrio aus Nasenschleim*" is said to have furnished "eine Musterkarte abenteuerlicher Runen und Schnörkel." *Bajardi* (1903), who studied *Weibel's V. lingualis* anew, obtained among many other forms branched threads, which stained like *B. diphtheriae* when treated with *Neisser's* method. The organism, therefore, is declared to be a "Streptothrix." The picture given by *Bajardi* (as original fig. 1) is reproduced as figure 85 on Plate VIII. The growth on gelatin resembled Anthrax, and in broth Actinomyces-like clusters were found. Large yeast-like cells also became visible, and in older cultures the long threads were again replaced by short cells, often containing polar granules.

Bonhoff (1896) isolated from water, besides other vibrios and spirilla, a "Vibrio Rugula" with 18–20 polar flagella, which also gave branching and on the plate Anthrax-like colonies. It is, no doubt, quite different from the anaerobic cellulose-destroying organism, described by *Prazmowski* (1880) under the same name, and mentioned on page 68.

Probably the first example of branching among the spirilla was the frequently quoted *Spirillum endoparagogicum*, discovered by *Sorokin* (1887–1890). The formation of branches in this case was due, according to the author, to the germination of "spores" inclosed in the mother cell, wherein they appeared in various numbers. How far this statement can be accepted as correct will have to be discussed in Chapter II. The drawing given in the first paper (1887) is reproduced as figure 29 on Plate H.

Spirillum Undula grows, as *Kutscher* (1895 *b*) found out, in a small and in a large type. The latter one showed all intermediate stages leading over to straight rods, as did also other spirilla. Sometimes *Kutscher* saw that one end of a cell was curved, while the other one was entirely straightened. He also noticed with *Spirillum Undula*, as well as with *Sp. Serpens*, what seemed to him to be "ganz eigenartige Gebilde," viz., curved branches breaking forth from

the side or from the end of a spirillum. He does not want to decide whether or not this is true branching. *Sorokin's* papers were evidently unknown to him.

Doerr had the opportunity to see the same process with *Spirillum pyogenes Mezinescu,* taken from broth as well as from the pus, as is demonstrated by the photographs accompanying his paper, but there is nothing said about it in the text. The "new" *Spirillum bataviae* described by *Faber* (1912) gave again "hornartige Ausläufer," and again the author feels unable to reach a decision whether these are branches or not.

Reichenbach (1901) met very clear examples of triangular cells in six days old broth cultures of *Spirillum rubrum.* Some of his photographs (original figs. 6, 8, and 9) are reproduced as figures 86 and 87 on Plate VIII. They are very similar to those published by *Severin* from his *V. denitrificans* and by *Bordoni-Uffreduzzi* from his *Proteus hominis capsulatus* which have been mentioned on pp. 55 and 59, respectively. Other branched cells of *Spirillum rubrum,* reproduced as figure 30 on Plate H from a drawing of *Meirowsky* (1914 *b*) are interesting counterparts to *Spirillum endoparagogicum* and to *B. radicicola. Spirillum tyrogenum Denecke* gave *Meirowsky* analogous results.

Concerning the morphology of the spirochaets only comparatively few data are available at present, as the numerous pure cultures isolated by *Noguchi* (1911–1912) have not been closely studied in this direction.

According to *Sobernheim* (1907, p. 536) atypical forms of *Spirochaeta pallida* are not infrequent in syphilitic tissue. He says:

> Abgesehen von ungewöhnlich zarten Spirochaeten, sowie von sehr kurzen Spiralen mit verhältnismässig lockeren Windungen, sieht man zuweilen Exemplare der Spirochaete pallida, die schleifenförmig gewunden und verschlungen sind. * * * Involutionsformen in gestalt von kurzen, deformierten Fragmenten, gekörnten spirochaeten-ähnlichen Gebilden, aufgeknäuelten und verklumpten Spirochaeten sind mehrfach beschrieben worden.

Castellani (1905) found in yaws besides, or instead of the spirochaets, oval irregular bodies, usually 5–8 μ, but also smaller or much larger ones. Analogous results were reported for syphilis by *Krzysztalowicz* and *Siedlecki* (1908) and by *McDonagh* (1912), which will have to be considered more fully in Chapter II. *Niessen* (1898), too, got Blastomyces-like growth from his "syphilis bacillus" or "Syphilomyces." It is absolutely impossible, however, to separate clearly the correct findings from the probably more numerous incorrect ones, contained in all of this author's publications. Contaminations, especially those of diphtheroid bacilli, have obviously played a conspicuous rôle in these investigations.

Branched growth of *Spirochaeta pallida,* as well as of *Spirochaeta balanitidis, stomatitidis,* and *gallinarum,* has been recorded by *Meirowsky* (1914 *a* and *b*). Some photographs published in his second paper (original figs. XI, 46, 55, and 56) are reproduced as figure 88 on Plate VIII. They show an exquisitely mycelial growth of *Spirochaeta pallida.* The occurrence of coccoid bodies within the life cycles of these and of other spirochaets have been ascertained by different authors; but, being evidently reproductive organs, they are to be considered in Chapter II.

With *Spirochaeta Obermeieri* granular and rod-like forms have been seen by *Karwacki* (1912). Whether the pathogenic bacillus, isolated by *Afanassiew* (1899) from a recurrens case, is to be accepted as a type of growth of the recurrens spirochaete, remains to be seen. It is reported to have grown first as a fine motile rod (0.3×1.5 μ), which later passed over into curved threads of 5–14 μ length, sometimes with pointed ends and granular structure.

Inada, Ido, Hoki, Kaneko and *Ito* (1916) have published some very interesting pictures of the ring forms, buds and branches of their *Spirochaeta icterohaemorrhagica,* found by them to be the causative agent of Weil's disease. Two of their drawings (original figs. 69 and 70 on pl. 61) are reproduced as figure 31 on Plate H.

The *Vibrio* (*vel Spirochaeta*) *suis,* which by *Rüther* (1910), as well as by *King* and his coworkers (1913), has been connected with hog cholera, grows according to the first-named author in comma or in the typical spirochaete form, which, however, occasionally divides itself into fine rods, resembling *B. influenzae* or *septicaemiae,* or assumes a Streptococcus-like appearance.

A problem which remains to be solved despite a considerable amount of work already done in this direction, is the question, whether the fusiform bacilli, practically constantly to be found in symbiosis with spirochaets in healthy organs, as well as in pathogenic processes, like angina, pyorrhea, stomatitis, gingivitis, noma, are merely symbionts or parts of the life cycle of the spirochaets.

The bacillus found by *Babes* (1893) to be connected with scurvey, causing gingivitis and hemorrhages, which grew only on agar first used by streptococci, presented the typical fusiform appearance, but gave also curved threads "longer and thinner than cholera bacilli." In a later publication (1907) of the same author analogous results are reported about angina. *Silberschmidt* (1901) described a fusiform bacillus from an abscess, exhibiting all intermediate steps leading over to thin spirilla, of which, however, no pure cultures could be made. *Beitzke* (1904) gave a summary of the work done up to that time, which together with own experiments led him to the conclusion, that fusiform bacilli and spirochaets belong together genetically. On account of the occasional occurrence of branched threads he is inclined to place these organisms in the neighborhood of Bang's necrosis bacillus and the Actinomycetes.

Wechselmann and *Loewenthal* (1905) noticed that in syphilitic tissue very thin rods with pointed ends and metachromatic granules may accompany the spirochaets. From microscopic studies upon angina *Mackie* (1905) drew the conclusion that the fusiform bacillus, the spirillum, certain sickle-shaped and some ribbonlike bodies, found in such material, "will all turn out to be different stages in the life cycle of one parasite." The most important contributions thus far made in support of the view that bacilli and spirochaets belong together are those furnished by *Ruth Tunnicliff* (1906–1915). Pure cultures of fusiform bacilli isolated (1906) from material taken from the mouth proved to be "extremely pleomorphous." Spirochaets appeared only temporary in large numbers, and being not easily stained they may have often remained unobserved, although being actually present. During the first 24 hours delicate pointed rods of 3–10μ length, often resembling the barred type of diphtheria bacilli, became visible. Some plumper bacilli ($1.5 \times 4\mu$) with deeply stained rounded ends also were seen. The next day long filaments developed, and soon afterwards spirals appeared, some of them also containing dark bodies. They usually showed pointed ends, were Gram-negative like the bacilli, and sometimes clearly made up of a chain of rods. Work done with the anaerobic *Bac. rhinitis* (1913–1915) confirmed and extended the earlier findings. In another paper by *Rosenow* and *Tunnicliff* (1912) the same dimorphism was described in regard to an anaerobic organism isolated from a fatal case of pyemia. The spiral forms were frequent in the fluid of condensation of serum agar. Coccoid forms, too, were present which, however, obviously are to be classed as reproductive organs. *Proca* (1908) saw satisfactory development of *B. fusiformis*, when it was grown in symbiosis with *B. subtilis* or with streptococci. Such mixed cultures produced in broth many spirilla with large, often unequal undulations and thin ends. On agar and gelatin, especially at the surface, the typical straight forms prevailed, while in the depth of the agar curved forms also appeared. The "*Cladothrix stereotropa*," found by *Proca* and *Danila* (1910) in syphilitic products, is said to have produced besides diphtheroid forms, fusiform bacilli as well as spirilla.

Shmamine (1912) thinks that the "nadelförmigen" bacilli ocurrring in syphilitic material are a type of growth of *Spirochaeta pallida*. Both organisms produce the same colonies, are identical in staining qualities, and the transformation of the bacilli into spirochaets was observed. These "needle-shaped" bacilli are considered to be different from *B. fusiformis*. *Carpano* (1914) obtained analogous results in his investigations upon the "fuso-spirilläre Symbiose" in necrotic gangrenous affections; and pure cultures of the spindle bacilli, isolated by *Klimenko* (1914) from scarlatina, gave also spirilla after a few transfers. Again both organisms stained in the same manner, and salvarsan acted upon these bacilli as it does upon the spirochaets. *Ozaki* (1915) found that a spirochaete from the human mouth in pure culture always produced straight bacilli, which, however, were taken to be not identical with *B. fusiformis Vincent*. In their report upon a fatal case starting from pyorrhea, in which the fusiform bacillus was

isolated from the blood, *Larson* and *Barron* (1913) also took the standpoint that bacilli and spirochaets belong together.

On the other hand, the opinion has been repeatedly expressed that spirochaets and bacilli are two different organisms, because they could be separated and kept for some time in pure cultures without showing any change in their morphology. *Ellermann* (1904–1907), *Vincent* (1905), *Mühlens* and *Hartmann* (1906), *Veszprémi* (1907), *Doflein* (1909), *Peters* (1911), *Lehmann* and *Neumann* (1912, p. 578), *Krumwiede* and *Pratt* (1913), *Kendall* (1916, p. 531), for instance, share this view. However, taking under due consideration in the first place the experimental difficulties, so often encountered with in growing these organisms on artificial substrates, in the second place the abnormal conditions prevailing in artificial cultures, and in the third place the analogous outcome of the very numerous experiments carried on with other organisms, apparently though incorrectly proving their monomorphism and constancy, it seems best not to discard too rashly the positive findings mentioned above, and to wait for further thorough and unbiased research. It can, e. g., not be accepted as justified that *Arnheim* (1914) rejects *Tunnicliff's* results in their entirety, though he himself observed the transformation of spirochaets into rod-like forms ("stäbchenartige Gebilde"), as well as the prevalence of the latter forms in some types of syphilitic eruptions. And when he lightly discards the round bodies, which he also had the opportunity to see, as "Zerfallsprodukte," he merely adds another unfounded assumption to the multitude of similar assertions concerning "involution forms, degeneration," etc. It is quite characteristic that *Tunnicliff* in her first work upon this subject, done together with *Weaver* (1905) also did not find any connection between fusiform bacilli and spirochaets, but that her later more searching investigations led to the opposite standpoint.

One point which needs emphasizing in this connection is the necessity to distinguish more sharply between the different bacilli included in this group than has been often done so far. The papers published by *Lewkowicz* (1906), *Babes* (1907), *Veszprémi* (1907), *Costa* (1909), *Shmamine* (1912), *Larson* and *Barron* (1913), *Ozaki* (1915) and others, furnish valuable material in this direction. It is very probable that some of these incompletely studied so-called fusiform bacilli have nothing whatever to do with spirochaets, while in other cases the opposite will be true.

A peculiar organism with a creeping motion, isolated by *Miehe* (1913) from leaves of tropical plants, and described by him as *Bact. repens*, seems to be related to those members of the Fusiformis group, whose character exhibits protozoon-like traits (cf. *Babes*, 1907). As figure 32 on Plate H two of *Miehe's* drawings are reproduced (from original figs. 9 and 10 on Pl. II). The curved, branched, and swollen, so-called involution forms duplicate very closely the similar growth of the spirilla.

(e) HIGHER BACTERIA (TRICHOBACTERIA, MYCOBACTERIA).

As organisms are included among spirochaets and fusiform bacilli, which evidently act as links connecting bacteria and protozoa, so among the so-called higher bacteria the relations become more and more apparent, which lead over to the fungi on the one side, to the algae on the other.

Many of the details collected on the preceding pages amply support the statement made on pp. 21–23 that all bacteria studied more thoroughly exhibit traits which so far have been generally considered to be characteristic for Actinomyces and some closely related organisms. Special genera (Actinococcus, Actinobacter, Actinobacillus) have been proposed, and it is a fact always to be kept in mind that especially the large endospore-forming bacilli of the Anthrax-Subtilis-Mycoides type are easily induced to enter a development very much resembling that of a typical Actinomyces. Some of the pros and cons in regard to a transplantation of Actinomyces and its relatives among the fungi have been mentioned already (on pp. 21–23), and others will be discussed in Chapters II and III. As some of the Actinomycetes are known to enter temporarily a motile stage, while others have thus far always shown themselves to remain permanently immotile, one might feel induced to accept this difference as the dividing

line between those belonging to the bacteria and those belonging to the fungi. In many cases, however, presence or absence of motility can not even be used as a means to separate bacteria (like *B. coli, dysenteriae, mycoides, subtilis, fulvum,* and others) into different species. Therefore it would be at least premature to use this mark as a basis for separating those organisms, at present all grouped together as Actinomycetes, into bacteria and into fungi. Thorough investigations upon their complete life cycles are also in this case quite indispensable before any well-founded decision can be rendered.

The same holds true concerning Beggiatoa, Cladothrix, Crenothrix and related organisms, which repeatedly have been declared to belong to the algae, not to the bacteria. Again this may be the case, but much of what is known at present seems to indicate their bacterial nature. As will be shown in Chapters II and III, it is especially their modes of multiplication and reproduction which connects them more closely with the bacteria than has been thought before. In fact, as Actinomyces has been declared (by *Claypole,* 1913) to be an "ancestral type" for bacteria, as well as for fungi, so Crenothrix, Cladothrix, Beggiatoa and related forms may be looked upon as prototypes, showing clearly such reproductive processes as occur also with all bacteria, though they nearly always have been overlooked thus far. It will be much more useful, therefore, if also these organisms will be made the objects of further bacteriological investigations, than to exclude them prematurely on account of insufficient systematic reasons. The general character of an alga, of a fungus, or of a protozoon is rather different from that of a Beggiatoa, of an Actinomyces, or of a Spirochaeta. Certainly these organisms are also more or less different from the majority of the bacteria, but just as some of their characteristic traits can be found with true bacteria, too, it seems best to retain them in their present position as "higher bacteria."

The organism described by *Bang* under the name abortus bacillus grows in the body as a fine small rod similar to *B. erysipelatos suum.* That the latter species is related to the Actinomycetes, has been emphasized by *Rosenbach,* who established for it the genus Erysipelothrix (see p. 52). That the abortus bacillus should take its place among the Corynebacteria, in the neighborhood of glanders, diptheria and diphtheroid organisms, has been pointed out by *Preisz* (1903). The cells growing in the cultures are either short, coccoid, sometimes very similar to the double-pointed forms of *Streptococcus lanceolatus,* or they are longer, thin, irregularly stained like the barred type of *B. diphtheriae,* passing over into wedge-, spindle-, and club-shaped forms. Y and more complex branching was found to be not infrequent. The Gram staining is said to have always given negative results. Interesting relations connecting this species with *M. melitensis* have been mentioned on page 44.

The necrosis bacillus of *Bang* is also to be placed here as being identical with the so-called *Streptothrix cuniculi,* described by *Schmorl* (1891). Cocci, motile and immotile rods, threads, branching and the formation of drumstick-like cells have been recorded by this author. Two of his photographs are reproduced as figures 89 and 90 on Plate VIII (from original figs. 2 and 5 on Pl. VII). *W. Ernst* (1902) did not find any motile rods, but he gives many details concerning the formation of branched threads, large inflations, ball-, pear-, and bottle-shaped cells.

The Streptobacillus described by *Tizzoni* and *Angelis* (1913–1915) as causative agent of pellagra, grows at first as motile thin rods, which break up into typical, but gram-negative, streptococci. These pass over into gram-positive staphylococci, which eventually reproduce rods. The latter were often found interspersed within the streptococcus chains. These, too, show branching; and clusters ("Drusen") with granular center and clubs at the outside also have been seen. The colonies made up by the cocci were flat, white, glistening, and liquefied gelatin.

That the glanders bacillus may be easily induced to change its character was emphasized by *Th. Smith* as early as in 1890. Acid reaction of the substrate caused a yellow-orange growth, while alkaline reaction made it grayish. A great variety of "puzzling involution forms" was noticed by this author. *Semmer* (1895) reported that glanders, as well as tubercle bacilli, are much inclined to form under saprophytic conditions threads which often show inflations, clubs,

and branches. The short rods are declared to be a type of growth adapted to the environmental conditions within the body. *Marx* (1899) secured further information upon the pleomorphism of this organism. Figure 33 on Plate H is a reproduction of his figures 1–4.

Galli-Valerio (1899, 1900) confirmed and extended these findings by a close study of the development of the glanders bacillus on different substrates and in the hanging drop. Small and large rods, clubs, dumb-bell-shaped and drumstick-like cells, as well as branching, were observed. The drumsticks alone are declared to be "involution" forms, not the others. The short small rods were found to appear in old cultures, after the large branched threads had disappeared. More data and pictures have been furnished by *Conradi* (1900). Branches appeared in his cultures already on the second day; basis and apex of the threads could be easily discerned. The organism is declared to belong to the Hyphomycetes. Excellent photographs, clearly illustrating the wide pleomorphism of *B. mallei,* have been published by *Carpano* (1913) and are reproduced as figures 91–96 on Plate VIII. As was emphasized by this author all the various forms appeared on the same substrate (acid glycerin horse-meat agar), which fact will be of special importance for future investigations upon the life cycle of this organism.

Before the etiologic significance of the diphtheria bacillus was fully established, repeatedly coccoid forms have been made responsible for this disease. It may be readily admitted that the presence of true micro- and streptococci might have caused some erroneous conclusions. Nevertheless, as new and well-founded observations have shown that the diphtheria bacillus is able to appear in a distinctly coccoid shape, those older findings deserve once more some interest. When *Oertel* (1871) directed the attention to the "micrococci" as causative agents of diphtheria, he cautiously pointed out that the "purely botanical problem concerning their true nature and relationship" should not be touched by him. He only made use of that name in the general sense as was done by *Hallier,* and he mentioned already that not only round but also long forms became visible which even were seen to sprout forth from round cells. With less precaution *F. Cohn* (1872 b) created a distinct species *Micrococcus diphtheriticus,* which later was transferred by *Zopf* (1885, c p. 53) into the genus Streptococcus. *R. Koch* (1878) also emphasized "that in diphtheritic deposits large numbers of micrococci are present," and he thought that probably the same cocci were active in pyemia as in diphtheria. *Baumgarten* (1890, p. 353) says:

> Es ist kein stichhaltiger Grund vorhanden, dem Streptococcus pyogenes die Anerkennung als eines Erregers der Hals- und Rachen-Diphtherie zu verweigern.

Guenther (1906, p. 577) takes a similar standpoint.

The pleomorphism of the true diphtheria bacillus was first studied by *Zarniko* (1889). He observed club-shaped cells, three- to four-fold longer than the normal rods, segmentation of the original bacilli, and the separation of these segments, which assumed spherical and ovoid forms. All these "atypical" cells were declared to be "involution" forms, though they were well and uniformly stained. *E. Klein* (1890–94) refuted this assertion. Club-shaped, as well as budding and branching forms, which he was the first to observe, are said not to be involution form, because they are present in young cultures and at the outbreak of the disease. The same holds true, as was stated in the second paper (1894), with regard to the spherical forms. In his monograph upon the diphtheria bacillus *Escherich* (1894) expressed the opinion that the branched cells present in the diphtheritic membranes, as well as in other parts of the afflicted throat, should be classed as secondary infection caused by a "Cladothrix," and he was inclined to accept as erroneous diagnoses those findings where cocci alone had been seen. Typical is, according to his opinion, the small wedge-shaped rod with rounded ends ($0.3–0.5 \times 1.2–2\mu$), which may pass over into elongated and clubbed forms. Spindle-, dumb-bell-, pear-shaped, as well as curved cells, were also seen. Moreover, from old cultures, as well as from the animal test, very long irregularly curved threads were obtained, which exhibited various inflations, some of them assuming the shape of chains of giant cocci. Weakly stained rods are declared to simulate sometimes streptococci, the chro-

matic granules taking the stain much better than the surrounding sheath. Concerning the relations existing between true diphtheria and diphtheroid bacilli *Escherich* takes the standpoint that both are strictly different, although he admits, of course, that the diphtheria bacillus may lose its virulence entirely.

His mistake concerning the absence of branching was soon corrected by a short paper published by *Fraenkel* (1895), wherein it is pointed out that the method usually followed in making the smear nearly always destroys the branched forms, which, however, are produced at least by some strains quite regularly in fresh serum or egg cultures. *Bernheim* and *Folger* (1896) soon confirmed *Fraenkel's* observations, while *Kanthack* (1896) directed the attention of the German bacteriologists to the fact that analogous results had been previously obtained in England by *E. Klein* and by himself. *Zupnik* (1897) noticed that not only the cell form, but also the form of the colonies of the diphtheria bacillus can vary to a great extent. Some of his strains were found to be motile. In 3–4 weeks old broth cultures *Madsen* (1897) observed many small and large, regular and irregular globules, which looked like a contamination by cocci. But all intermediate stages leading over to the clubbed rods were visible, and plate cultures showed that the strains were pure diphtheria bacilli. More details concerning the branching of the diphtheria bacilli were furnished by *Kurth* (1898). The club-shaped form of the branches shown in his pictures makes an exact duplicate to the drawings of branched streptococci, published by *Babes* (1895) and reproduced as figure 3 on on Plate B. He thinks that such forms are restricted to the true diphtheria bacillus, and that they could be used, therefore, in differentiating from the pseudo-diphtheria group. Evidently he was unaware that *Babes* (1895) had already given the analogous pictures of diphtheroid organisms, reproduced on Plate J as figure 34. Very interesting is the observation of *Kurth* that in symbiosis with *Streptococcus lanceolatus* the diphtheria bacilli became so similar to them, that they hardly could be distinguished. *Meyerhof* (1898) once more discussed the great pleomorphism of the diphtheria bacillus, and confirmed that branching is very frequent on egg substrates. Very careful studies upon dividing and branching of the diphtheria bacilli have been made by *Hill* (1899, 1902), who for this purpose made use of his newly developed "hanging agar block" method. With young cultures he succeeded in observing directly the "snapping off" of oval side branches and their stretching out to normal rods.

It was by no means in accordance with the facts known at that time, and in part without logical foundation, too, that *Migula* (1900, Vol. II, p. 499) wrote concerning the diphtheria bacillus:

> Dass diese Verzweigungen . . . nichts weiter als Involutionserscheinungen sind, braucht wohl nicht erst besonders hervorgehoben zu werden . . . Überhaupt ist der Diphtheriebacillus sehr leicht zur Degeneration in morphologischer Hinsicht geneigt, und dies umso mehr, je besser er sich an die künstliche Kultur gewöhnt hat.

Weesbrook, Wilson, and *McDaniel* (1900) arranged the different forms shown by the diphtheria bacillus into seven types; each of them containing cells of granular, barred, and solid staining. Granular forms were found to predominate at the beginning of the disease. The resemblance to *Streptococcus lanceolatus* is very pronounced in types D and G. As *A. C. Abbott* remarked in the discussion following the reading of this paper, representatives of all seven types probably occur in every culture. Many of them, however, are according to his opinion "simply involution forms." Their appearance is greatly influenced by the hydrogen ion concentration of the substrate (*Bunker*, 1917). *Cache* (1901) reported upon another case of considerable persistency in branching in successive subcultures, and *Concetti* (1901) secured further information upon the reciprocal relation between virulence on the one side and club formation, branching, and luxuriance of growth on the other side. Under anaerobic conditions the Actinomyces-like forms could be reverted to the typical rod of high virulence. Additional data in this direction are to be found in a paper published by *Ohlmacher* (1902), some of which were accepted by the author as proof of the possibility of changing true diphtheria into pseudo-diphtheria bacilli. As was mentioned on p. 47, a puzzling "streptococcus" also was found, which in various directions came very close to the character of a member of the diphtheria group.

Beck (1903) thought that the club-shaped form should be considered to be the normal type of growth of the diphtheria bacillus; branching again was found to be frequent in young cultures. A picture of a 1-day-old growth on agar (l. c. p. 765, fig. 1) shows clearly small and large globular and oval forms. *Spirig* (1903) got typically Actinomyces-like growth from old diphtheria cultures: long thin threads dividing up into rods and cocci, forming a white powdery ("kreidig") layer on the surface. But at the same time he revoked an earlier statement of his (1899) concerning the development of branched threads. They were now declared to have been those of a contaminating "Streptothrix," just as had been assumed by *Escherich* (1894) in analogous cases (see above, p. 77). *Goodman* (1908) discussed fully the great morphological and physiological variability of the diphtheria, as well as of the pseudo-diphtheria, bacilli. He comes again to the conclusion that all be "but variants of a single species, *B. diphtheriae*, which constitutes the entire group." The facts secured by *Smirnow* (1908) concerning the growing of *B. diphtheriae* in coccoid form, when living together with streptocci and other bacteria, confirm the analogous findings of *Kurth* (1898), mentioned above. *Cappellani* (1910) encountered repeatedly in the beginning of the disease in fresh exudate highly virulent diphtheria bacilli showing good branching, which was reproduced in the transfers on different substrates. He supposes again, like *E. Klein* (1890), that the rods are merely adaptations to the parasitic life, while the actinomycotic growth is the normal development under saprophytic conditions.

In the course of diphtheria tests made in Hamburg, *J. Dale* (1910) repeatedly met with unusual miscroscopic pictures, as shown in figure 97 on Plate IX (reproduced from original fig. 6). This photograph makes an interesting counterpart to figure 91, coccoid forms of *B. mallei.* The secondary colonies, which developed from such coccoid growth. were again made up of typical diphtheria bacilli. Soon afterwards *Balfour* (1911 *d*) reported that in the tropics clinically true diphtheria cases frequently are caused by pure cultures of curious cocci, showing *Neisser's* granules and developing characteristic diphtheria colonies on Loeffler's serum, which, however, are composed exclusively by Gram-negative cocci. In subcultures on agar typical rods were found within 48 hours, while on serum the cocci remained constant. The photographs appended to the paper are quite similar to that of *J. Dale.*

A study of the diphtheria group (including pseudo-diphtheria bacilli) by the biometric method was made by *Morse* (1912). Six morphological types are described and correlated with cultural and biochemical characteristics (chromogenesis, acid production, virulence, toxin production and complement fixation). They are arranged in two main subgroups: (1) true diphtheria bacilli—(*a*) virulent, (*b*) avirulent; (2) diphtheroids, to which reference will have to be made below. *Berry* and *Banzhaf* (1912) were unable to confirm the results recorded by *Goodman* (1908) mentioned above. They explain them by assuming that Goodman had worked with a "mutating organism." Their own experiments show very wide and irregular variations in the production of acid, despite the title of the paper: "Nonvariability of Diphtheria Bacilli."

That, in fact, the variability of these organisms is by no means inferior to that of other bacilli has been fully demonstrated anew by *Baerthlein* (1913), by *Bernhardt* and *Paneth* (1913), and by *Schmitz* (1916). *Baerthlein* noticed many changes in 2–4 weeks old cultures, which seemed to him to be examples of true "mutation." Three types of colony and cell form were found to be regularly present. *Bernhardt* and *Paneth,* as well as *Schmitz,* conclude from their observations upon the morphological and physiological variability of the diphtheria bacillus in cultures and in the body, that true and pseudo-diphtheria bacilli are to be accepted as strains of one species. Secondary colonies were especially inclined to furnish aberrant forms. That the inoculation into the animal is very efficient in bringing about such changes, as was observed by these authors, has been confirmed by *Römer* (1914). *Park* and *Williams* (1914, p. 38) mention the fact that "many large, intensely staining forms with one to several apparent branches and many metachromatic granules" were usually present in 6–12 days old cultures, and that they were the only ones which showed active growth and division. The same authors also give (l. c., p. 294, fig. 119) an interesting picture of a strain which grew exclusively in the form of a large coccus. *Heinemann* (1917) found irregularities in toxine production connected with variations in growth and in microscopical appearance. Strains of low toxicity

gave thick yellowish films, which were composed of diplococci, resembling strepto-and meningococci. The great importance of this observation for the correct diagnosis of diphtheria is emphasized by the author, who evidently was not aware of the fact that he once more confirmed what had repeatedly been discovered by several independent workers. A very complete description of the wide pleomorphism of the diphtheria bacillus was published by *Bergstrand* (1918). The occurrence of various globular forms was also thoroughly studied in this case.

The relations existing between streptococci and pseudo-diphtheria bacilli were pointed out by *Babes* in 1895. As figure 3 on Plate B his drawings of branched streptococci, showing club formation, were reproduced. They make an interesting counterpart to his sketches of clubbed pseudo-diphtheria bacilli, reproduced as figure 34 on Plate J (from original fig. 3). How the bacilli may pass over into "streptococci," is also well discernible in these early drawings. *Escherich* (1894 p. 190-225) was the first to show that the diphtheroid organisms are not less pleomorphic than the true diphtheria bacilli. When *Seitz* (1896) isolated several streptococci from the mouth, he also got one strain which was considered to be an avirulent diphtheroid. Its colonies were entirely like those of the streptococci, its cells showed globular, triangular, rodlike, club-shaped, and many other irregular forms. The staining with Gram's method gave positive, as well as negative, results. Early observations upon branching of pseudo-diphtheria bacilli have been recorded by *Kanthack* (1896). A "Bacterium diphtheroides," isolated by *E. Klein* (1900) from the pus of a diseased udder, grew in serum mostly in globular or ovoid form, while only a few wedge-shaped rods indicated its true character. *Nakanishi* (1900 *c* and *d*) made a diphtheroid from the skin the object of very careful studies, because for some time he believed to have discovered the causative agent of variola. It started its growth as triangular coccus, later stretched out into short and long rods, which became beaded and eventually turned over into club-, dumb-bell-shaped or branched forms. These sometimes remained constant in successive transfers. In the animal test bright globular or oval bodies appeared, which in artificial substrates assumed again the bacillary form. Those shown in figure 98 on Plate IX (reproduced from original fig. 8) invite a comparison with the coccoid growth of diphtheria and glanders bacilli (figs. 96 and 91).

When discussing the question of virulence among pseudo-diphtheria bacilli *Hamilton* (1904) admitted that usually the differentiation from the true diphtheria bacillus is not too difficult. But he also noticed that some virulent pseudo-diphtheria bacilli may become so similar to true diphtheria bacilli, that they can only be distinguished by animal experiments. *Clark* (1910), on the other hand, is of the opinion that so-called virulent pseudo-diphtheria bacilli are true diphtheria bacilli of atypical morphology. *Bac. Hofmanni,* however, is declared to be a different species, not merely a variety of the Klebs-Loeffler bacillus, though, according to the author, both "doubtless" came from "common ancestors." *Kolmer* (1912) considers the Hofmann bacillus to be a "mutation" of the diphtheria bacillus, connected with it by many intermediate forms. Wesbrook's types were studied anew, and the sugar test accepted as of practical value, "when used in conjunction with tests for virulence." *Morse* (1912) added to *B. Hofmanni* and *xerosis* as two new types of diphtheroids the pink growing "*B. hoagii*" and the yellow "*B. flavidus.*" As mentioned above, *Bernhardt* and *Paneth* (1914) concluded from their experiments, that true and pseudo-diphtheria bacilli are strains of one species. Likewise *Trautmann* and *Gaethgens* (1913) report to have succeeded in changing experimentally avirulent diphtheroids to fairly virulent typical diphtheria bacilli.

From cases of Hodgkin's disease *Lanford* (1914) isolated a pink, highly pleomorphous organism of doubtful etiological significance, which assumed various shapes and sizes, from a cocco-bacillus, 1–2μ, to a large raquet-shaped bacillus, 8–10μ in length. In older cultures rods of about the size of *B. Hofmanni* were predominant. Occasionally relatively enormous oval forms became visible. The most complete work upon the morphology and the life history of various Corynebacteria, especially of several strains causing malignous granulom (Hodgkin's disease), which has been done so far, is that of *E. de Negri* and *Mieremet* (1913) and *E. de Negri* (1916). Single-cell cultures were used for these investigations which, as was already pointed out in our first paper (*Löhnis* and *Smith,* 1916 *a,* p. 696), represent a very welcome confirmation

and extension of our own observations upon the life cycles of the bacteria. Some of *Negri's* photographs, published in her second paper, are reproduced as figures 99–101 on Plate IX (from original figs. 11, 12, 30, and 73), showing granular forms from whey agar, threads from serum, round cells and thin rods from serum, together with a yeast-like cell from granulom (magnification in all these cases × 560). The pathogenicity of the last-named cell form is especially noteworthy. That *Negri* erred in placing her organism among the Blastomycetes has been discussed before (*Löhnis* and *Smith* 1916, *a*, p. 697). It is not improbable that at least some of the so-called bottle bacilli from the skin, which are of a rather uncertain systematic standing (see p. 22), are analogous types of growth of common diphtheroids

The close relations existing between this group and the streptococci have been made the object of more thorough studies by *Walker* and *Adkinson* (1917) and by *Mellon* (1917). The organism, isolated by the first-named authors from sputum of patients with bronchial asthma, produced different types of colonies on plain and on dextrose agar. Some of them were very small, opalescent, looking like tiny dew drops; they contained streptococcus-like forms, Gram-positive, as well as Gram-negative, within the same chain. Under certain conditions they passed over into diphtheroid bacilli, while in other cases they remained fairly constant. Frequently a chain was made up of Gram-positive and Gram-negative cocci, oval forms, and true rod-shaped bacilli. The authors are convinced that "many of the streptococci found in sputum may be really diphtheroid organisms rather than true streptococci, and this may even apply to the hemolytic streptococci." Another type of colony was dirty white, raised in the center, and with undulate margin. It contained chiefly Gram-positive bacilli, but also Gram-negative bacilli, cocci and diplococci. Still another type was large, round, flat, thin, whitish and very tenaceous. In it usually Gram-positive cocci predominated, some of which were very large. *Mellon's* strain was isolated from the lung (pulmonary fibrosis). When grown in broth containing a few drops of human or rabbit serum, the bacilli of the barred type disintegrated, and their chromatine masses became diplococci, as shown in figure 35 on Plate J (reproduced from original fig. 2, p. 88), which later grouped themselves either as staphylo- or as streptococci. It was difficult to revert these cocci into the original barred rods, but this was done successfully on slightly acid, as well as on comparatively strongly alkaline, substrates. In the animal this organism also acted like a streptococcus of low virulence. *Mellon* mentions especially the relations connecting his strain with *Thiercelin's* Enterococcus. A glance over the foregoing pages, as well as over the references given on pages 46–48 in regard to the diphtheroid growth of various streptococci, will suffice to demonstrate in addition, that analogous relations between numerous members of both groups are indicated in many of the earlier publications. In the third part of *Mellon's* paper the name *B. enzymicus* was proposed for the subgroup related to the streptococci; it was found to be present everywhere in the body. Other diphtheroids displayed some proteus-like characteristics; they were motile and liquefied gelatine. *Eberson* (1918) believes that the diphtheroids should be separated into not less than nine groups, all of them having the character of true species. With regard to *B. enzymicus* it is assumed that the presence of coccoid forms is either due to a contamination, or they are, indeed, produced by the diphtheroid organism; in this case, however, the author does not want to have them classed as "true" cocci.

B. leprae was introduced into the literature by *G. A. Hansen* (1880–1882) and *A. Neisser* (1881) as a slender motile bacillus, forming round "spores." *Babes* (1883) saw frequently round swellings at the end of the rods, and in the tissue between the rods small round elements (0.5–1.5μ) in small groups or chains, which stained the same way as the rods. Another early but little known contribution was made by *Lutz* (1886), who noticed that after careful decolorization (with alcohol + nitric acid) of a strongly stained preparation (Gram's method was especially useful for this purpose) all bacilli presented themselves as chains of well stained cocci within weakly stained sheaths. Really homogeneous rods were never seen by him. Sometimes at the end of the rods, or separated from them, other larger round bodies became visible, either very darkly stained or not at all, or reacting like metachromatic granules. That some

of these were reproductive cells was discussed by the author and will be considered in Chapter II, while other still more interesting observations are to be reserved for Chapter III. Some of *Lutz's* drawings are reproduced as figure 36 on Plate J (from original figs. 7–11 on p. 81). He proposed to place the leprosy organism in a special genus Coccothrix, which also had to embrace the tubercle bacillus and related forms. *Bordoni-Uffreduzzi* (1888 *a*) noticed that homogeneous or granulated rods became visible in his preparations, according to the mode of staining employed. In addition to the round swellings at one end of the rods, he met also dumb-bell-shaped cells.

In 1897 *E. Levy* described for the first time an only slightly acid-resistant Actinomyces-like organism, related to *B. tuberculosis*, which was isolated from a case of leprosy. More details upon this organism were given by *Czaplewski* (1898). Young cultures contained homogeneous acid fast rods; in older material the granules only were stained within the decolorized bacilli. In broth thick round bodies were formed in the middle or at the end of the rods; clubs and branches became also visible, the latter especially in gelatin. The etiological significance of the organism was left in doubt. Similar diphtheroid strains were secured by *Teich* (1899) in five different cases, which grew either as thin rods, like in the tissue, or displayed the wide pleomorphism characteristic for this group.

Barranikow (1900–1902) was the first to state that the leprosy organism is characterized by a "complicated life cycle." Form, staining reaction, acid-resistance, and virulence were found to be different in the various phases of life. Washing with water was sometimes sufficient to take away all stain. *Kedrowski* (1901) confirmed that leprosy like other so-called acid-fast bacilli are by no means constantly acid-resistant, and he also confirmed the wide pleomorphism of this species. Cocci, rods of different shape and size, clubs and sometimes typically Actinomyces-like growth were observed. Young bacilli proved to be motile. The author states that like plague, glanders, diphtheria, and tubercle bacilli so also the leprosy organism passes through a complicated life cycle outside of the body, and that the branched forms are one of the stages of growth entered at this time. *Kedrowski* continued his investigations for a long time, and in a second paper (1910) he was able to furnish much additional proof concerning the pleomorphism, but also concerning the etiological significance of his organism. Figure 37 on Plate J (a reproduction of original fig. 37) demonstrates clearly the "Coccothrix-," as well as the Actinomyces-like, habit of growth.

The discoverer of the leprosy bacillus, *G. A. Hansen* (1903), however, was not inclined to accept any of these cultures as genuine leprosy organisms. He could not turn his mind from the striot monomorphism, in vogue at the time when he made his discovery (1879). Changes in form, acid-resistance, and especially the occurrence of branching were to him convincing proof of untrustworthy investigations. This anachronism was rectified a few years later by another paper on the same subject, published in the same "Handbuch," by *Babes* (1907 *a*).

The results of extensive investigations carried out in British India, published by *T. S. Williams* (1911), are in complete agreement with *Kedrowski's* work. The "*Streptothrix leproides*," as it is called here, grows as bacillus or Streptothrix (i. e. Actinomyces) of changing acid-resistance. The excellent pictures accompanying the paper show also coccoid forms. In his "Études sur les Actinomycètes" *Galli-Valerio* (1912) gave some interesting drawings of clubbed and spindle-shaped cells of *Mycobact. leprae*, as taken from the tissue. Making use of single-cell cultures, *Reenstjerna* (1912) proved definitely that a culture of the leprosy organism, whose pathogenicity was established by experiments on monkeys, was able to grow temporarily as a not acid-resistant streptococcus. *Kritschewsky* and *Birger* (1912) made some serum tests, which indicated that *Kedrowski's* culture was the true *B. leprae*, while another culture from *Duval* did not react with these sera. A very thorough discussion of the whole subject is contained in two papers by *Wolbach* and *Honeij* (1914), who are of the opinion that in the different parts of the world apparently different varieties are acting as causative agents: (*a*) the diphtheroid, (*b*) the acid-fast pigmented, and (*c*) the acid-fast not pigmented groups. Their own culture once more exhibited an "extreme pleomorphism." In young cultures short coccoid, not acid-fast forms in pairs were prevalent, but acid-fast granules and segments were also al-

ways visible. In addition, not acid-fast slender rods with acid-fast granules (i. e. *Lutz's* "Coccothrix") and club-shaped cells, whose swollen ends were usually acid-fast, were present. Inoculation experiments and agglutination tests were considered not to be conclusive.

On the other side, the standpoint taken by *G. A. Hansen* was defended by *Duval* and his collaborators. In 1912 *Duval* and *Wellman* described a nonchromogenic, constantly acid-fast rod, morphologically resembling the diphtheria bacillus, which grew only on specially prepared substrates, and whose etiological significance seemed to be probable. The pleomorphism observed by other authors was contested. In 1913 *Duval* and *Harris* pointed out anew that the acid-fast character of their culture was "as constant as that of *B. tuberculosis*" (which they apparently assume to be constant) and that no streptothrical and filamentous stages became visible; only diphtheria-like "involution" forms were recorded. In 1914 *Duval* extended and confirmed these statements: All his cultures grew constantly as acid-fast rods. Those, however, which did not adhere to this "legitimate" course, were discarded as contaminations, though no proof was available to support this assumption (see the quotation given on p. 20). In addition, in 1915 *Harris* and *Wade* did not only demonstrate that diphtheroids are to be found everywhere on and in the body, in air, water, etc., and that those isolated by them were again entirely constant, they also did not hesitate to take these findings as a basis for the assertion that the opposite results, obtained by all other authors, were simply to be explained as caused by impure cultures. A fitting remark, made by *Bayon* (1915) in regard to such an assumption, was quoted on page 21. More recently *Duval's* standpoint has been made quite untenable by the work done by *Johnston* (1917), who declares himself wholly in accord with *Kedrowski* and *Bayon*. He states that the leprosy organism has two stages in its life history: a streptothrical not acid-fast form, and a bacillary acid-fast one.

The pleomorphism of *B. tuberculosis* was emphasized as early as in 1883 in two publications by *Klebs*. While *R. Koch* (1882) strongly insisted upon the constancy and the monomorphism of his bacillus, and the presence of these bacilli was declared by him to be the only valid proof of true tuberculosis, *Klebs* pointed out, that always, even in *Koch's* own cultures, coccoid forms were regularly to be found, some of which seemed to be motile. The bacilli are, according to his opinion, one type of growth of the tubercle organism, and their presence is declared to be undoubtedly of great diagnostic value. As causative agent, however, the cocci are considered to be of the same, or even of higher, importance. Observations published by *Babes* (1883) at the same time fully confirmed this view. Not infrequently no bacilli could be found in tuberculous tissue, but "grains bien colorés, ronds ou cubiques, se rapprochant de l'apparence des sarcines". These round bodies were, as in leprosy, 0.5–1.5μ in diameter; they were stained in the same manner as the rods. The bacilli were also seen to contain sometimes round inflations in the middle or at the end. In the same year (1883, p. 67) *Zopf* emphasized that, despite *Koch's* statement, the tubercle bacillus may assume the form of a coccus. The critique directed by *Flügge* (1884) against *Zopf* remains an interesting document of the manner in which the monomorphistic dogma was established and defended at that time. But at the same time *Biedert* and *Sigel* (1884) emphasized once more that in chronic cases the regular bacilli may be entirely replaced by granular rods and accumulations of "granules" not stained by aqueous aniline dyes, but stained by a modified Gram method.

In 1883 and 1884 *Malassez* and *Vignal* also published their important papers on "tuberculose zoogléique, forme ou espèce de tuberculose sans bacilles." Like *Klebs* and *Babes*, they often found during several transfers in the animal test only "masses zoogléiques de micro-coques"; then the bacilli appeared, and later they disappeared again. In their first paper the authors state clearly: "Il existe une parenté entre nos zooglοées et les bacilles de Koch." In the second paper, however, they leave this point open to further research. Their drawings show, that the micrococci, which they observed, were sometimes considerably larger than the round bodies inside of the bacilli. Several authors have later assumed that this "tuberculose zoogléique" of *Malassez* and *Vignal* had been some kind of pseudo-tuberculosis, an assumption which is evidently not in accordance with the facts reported by the French bacteriologists, and which is likewise contradicted by the more recent observations of *Spengler*, *Much* and others

to be mentioned below, which fully confirm those older discoveries. After *Lutz* (1886) had noticed that the tubercle bacilli, when treated in the same manner as he did with the leprosy bacilli, also assumed the appearance of a "Coccothrix," *Klebs* (1887) modified somewhat his earlier standpoint; he now thought that the coccoid forms which he had seen, should be also declared as "Coccothrix." This explanation, however, is not in full agreement with those observations which revealed the presence of single, comparatively large, globular, acid-fast bodies in tuberculous tissue. Fig. 102 on Plate IX is a reproduction of a sketch published by *Cornil* and *Babes* (1890, Vol. II, p. 402, fig. 342) of a cut through the pia mater in tuberculous meningitis, showing such "grains ronds qui se colorent par le même procédé que les bâtonnets."

That the tubercle bacilli may pass over into branched forms was first ascertained by *Metchnikoff* (1888*a*) for the avian type. Cultures kept at 44° C. exhibited a great pleomorphism, as shown in figure 38 on Plate J (reproduced from original fig. 20 on Pl. V). That the branching is the result of budding is clearly visible in the picture, as is also the occasional separation of oval side branches (*s* and *n–n'*), i. e., the same process which was described later by *Hill* in regard to the diphtheria bacilli. It was emphasized by *Metchnikoff* that the branched forms should not be classed as "involution" forms. More data upon branching also of the human and bovine types of the tubercle bacillus have been contributed during the next years by *E. Klein* (1890–1894), *Mafucci* (1892), *Fr. Fischel* (1893), *Coppen-Jones* (1893–1895), *Bruns* (1895), *Semmer* (1895), *Kanthack* (1896), *Olsen* (1897), and *Marpmann* (1897). Most of these authors reached the conclusion that the bacilli are merely a type of growth of an organism which should be classed among the Actinomycetes or even among the higher fungi. (See p. 21.) Club-shaped cells were very frequently found by *Coppen-Jones* in sputis from far advanced cases. *Babes* and *Levaditi* (1897) were the first to produce experimentally typical Actinomyces-like clusters ("Drusen") with clubs in the animal tissue. Their results were soon confirmed by *Schulze* (1899) and by *Lubarsch* (1899).

Ferrán (1897*a*), on the other hand, reported that by successive adaptation of the tubercle bacilli to ordinary broth (without glycerine) he had been able to reduce their acid-fastness and to induce them to grow at 20° or even at 10° C. as motile coli-like rods, which, however, were still able to produce typical tuberculosis in guinea pigs, simultaneously reverting to the original type of growth. Temporary motility in young homogeneous cultures was also recorded by *Schumowski* (1898–1899), by *Courmont* and *Descos* (1902) and by *Hawthorn* (1903*a*).

Schürmayer (1898) encountered small and large nonacid-fast globular forms of the avian type, which reproduced typical rods. Some pictures presenting Streptococcus-like, but still acid-fast growth in scrophulous glands, which were published by *Arrigo* (1900), are reproduced as figures 103 and 104 on Plate IX (from original figs. 1*a* and 2*b*), where they make a sharp contrast to the richly ramified thread in figure 105, reproduced from a photograph made by *Migula* (1900, Vol. II, fig. 3, Pl. V), who had "no doubt" (though, of course, also no proof) that such abundant growth is "merely degenerate." *Dorset* (1901*a*) found another good example of budding and branching of the human type in a 6-weeks-old glycerine broth culture. The bovine type, when cultivated in the frog by *Herzog* (1903), changed its morphology to such an extent that, as the author says, it seemed to be very doubtful at first whether the forms observed were really merely transformations of the organism tested. *Wolbach* and *Ernst* (1903), too, found the morphological variability of the tubercle bacillus under different conditions and especially in rapidly growing cultures "most extensive," leading from small cocci up to long threads and large branched forms.

The greatest deviation from the "legitimate" form, which had been declared by *R. Koch* and his followers to be the decisive indication of true tuberculosis, was probably that described by *Schroen* (1904). According to this author the tubercle bacillus passes through three different developmental cycles whose complete description, though promised in this paper, apparently has not been published. The causative agent of phthisis is considered by *Schroen* to be an organism of peculiar standing and not to be connected with the tubercle bacillus, which is accepted as only causing tuberculosis, not phthisis. Description and pictures of this "new phthisiogenic microbe," as it is called, leave, however, not much doubt that they actually refer

to a type of growth of the tubercle bacillus, analogous to that produced by *B. radicicola* within the root nodules, but never on artificial substrates. As this will be discussed in Chapter III, the discoveries of *Schroen* will also better find their place there.

In a paper entitled "Polymorphisme du bacille de Koch dans les produits de l'expectoration phthisiques" *Piery* and *Mandoul* (1904) established the following four morphological types: "(1) les homogènes courts, (2) les homogènes longs, (3) les moniliformes courts, (4) les moniliformes longs." Like *Lutz*, these authors are of the opinion that the tubercle bacilli are made up of chains of well stainable granules, which are surrounded by sheaths of variable stainability. According to *Péju* and *Rajat* (1907) successive cultivation of the tubercle organism in broth containing up to 4 per cent potassium iodide proved to be very efficient in stimulating lateral budding and multiple branching, as well as the production of other aberrant nonacid-fast forms. Large inflations of 6–8 μ diameter and typical mycelial growth were also observed. Analogous results were secured by *Arloing* (1908) by keeping the cultures at 44.5–45.5° C, and under increased atmospheric pressure (2.5 atmospheres). *Miehe* (1908) made some observations upon branching of the tubercle bacillus in the hanging drop. The globular and ovoid bodies were again accepted by *Betegh* (1908) as the initial stage in the development of the tubercle bacillus. They were seen by him to produce very thin, straight, nonacid-fast rods, which increase in size, become acid-fast, and assume usually a somewhat curved shape. These rods, first homogeneous, later become granular, and finally disintegrate again into these round bodies. *Much* (1907–1909) made some new attempts to convince the German bacteriologists, that *Koch's* monomorphistic dogma was indeed not in accordance with the facts. Once more the infectious nature of the coccoid type of growth and the occurrence of tuberculosis without the "legitimate" tubercle bacilli were clearly demonstrated. The passing over of acid-fast into not acid-fast forms and the opposite process were also closely studied.

Probably thus far the most complete investigation upon the life cycle of *B. tuberculosis* has been made by *Maher* (1910–1915). The transformation of the typical rods into granular forms, the loss of acid-resistance, the passing over into filamentous, coccoid, and yeastlike cells, and the regeneration of not acid-fast, as well as of acid-fast, rods were carefully followed. Of special interest, however, are the discoveries made by this author in regard to the symplastic stage of the tubercle organism, which will be discussed in Chapter III. The coccoid, as well as the yeastlike, cells could again be cultivated as such, in the same manner as it was done, for instance, with the Corynebacteria by *E. de Negri*. Unfortunately, only rather short reports have been published by *Maher;* and several hypotheses incorporated in his papers (assuming, e.g., the tubercle bacilli to be the offspring of the acid-fast spores of *B. subtilis*, and meningococci, as well as pneumococci, to be the progeny of the tubercle bacilli) evidently have had the effect that his discoveries did not elicit adequate attention.

Much's work has been confirmed and extended by *Krylow* (1911), who noticed that in vitro, as well as in vivo, very young tubercle bacilli were not acid-fast and also Gram-negative, but could be easily stained with aqueous aniline dyes. The Gram-positive substance, i. e., the granular mass, is the next to be developed, while the acid-fast material appears later within the membrane. The pleomorphism again was found to be very conspicuous already in young cultures. Analogous results were recorded by *Klepzoff* (1912), who points out that these changes seem to indicate relations connecting the *B. tuberculosis* and the Pasteurella groups. From the latter he was able to get acid-fast growth, too. Several interesting drawings of branched threads and of clubbed forms of *Mycobact. tuberculosis* have been published by *Galli-Valerio* (1912); and more details concerning the variation in acid-resistance and cell morphology may be found in a paper by *Wherry* (1913 *a*) upon the "Chemical Conditions Influencing Acid-Proofness and Non-Acid-Proofness in a Saprophytic Culture of *B. tuberculosis*." Minute, as well as large, coccoid bodies, short and long, thick and thin, straight and curved rods, which were or were not acid-resistant, were all seen to occur in an old culture originating from *R. Koch's* laboratory.

The pleomorphism of the pseudo-tubercle bacilli is very similar to that of the genuine tubercle bacillus. *Preisz* (1894) published some interesting pictures of a strain isolated from

sheep, reproduced as figures 106 and 107 on Plate IX (from original figures III–V on Plate IX, all × 1,000), showing their diphtheroid growth, as well as a Streptococcus-like development, which practically duplicates that found by *Arrigo* with *B. tuberculosis* (fig. 103, Pl. IX). The pseudo-tubercle bacillus isolated by *Korn* (1899), from butter, showed in the cultures, as well as in the animal test, traits characteristic of the tubercle bacillus on the one side, of *B. coli* on the other. The "Coccothrix" form dominated in old agar and serum cultures. Branched, club-shaped and spermatozoid cells were also seen. Motility in young cultures was noticed by *Moëller* (1899) with his "Grass bacillus II." *E. Klein* (1899) did not see active motility, but also his culture showed two polar flagella when stained with *Ermengem's* method. Typically actinoymyceslike clusters ("Drusen") in the animal test were obtained by *Lubarsch* (1899) with pseudo-tubercle as with genuine tubercle bacilli. The organism described by *Bongert* (1901) under the name *Corynethrix pseudo-tuberculosis murium* exhibited an analogous behavior, and the author points out that this club formation is a normal mode of growth, not a sign of degeneration. *Moëller's* grass and hay bacilli were also seen by *Abbott* and *Gildersleeve* (1902) to grow in the tissues very much like Actinomyces and *Bac. tuberculosis.* All pseudo-tubercle bacilli tested by *Courmont* and *Descos* (1902) proved to be actively motile, like *B. tuberculosis*, in young liquid, homogeneous cultures. The partially acid-proof "Streptothrix," isolated by *Schabad* (1904) from a case of pseudo-tuberculosis, produced neither clubs, nor clusters, but it showed very clearly true branching. A close relationship to the true tubercle organism was noticed by *Sanfelice* (1905) when he studied another "Streptothrix," causing pseudo-tuberculosis.

Mycobacterium hyalinum and related species, whose peculiar physiological activity as benzine, petrol and paraffin destroyers has been investigated by *Söhngen* (1913), appeared in many respects very much like Actinomyces. On the other hand, however, they also resembled *B. radicicola,* growing in the same type of colonies and in the form of Y-shaped rods.

A fairly complete description of the morphology of Actinomyces in man was published by *J. Israël* as early as in 1878 in a paper discussing for the first time human actinomycosis. He enumerates as elements building up the clusters found in the pus: (1) thin threads; (2) granules of various size, some small like typical cocci, others larger, very bright, globular or oval; (3) peculiar pear- or club-shaped bodies of very variable size and form, apparently dividing longitudinally. Sometimes the granules alone were present in the tissues. All intermediate stages connecting threads and clubs were seen. Formation of buds was noticed, too. One of *J. Israël's* drawings (orig. fig. 4 on Pl. II) has been reproduced as figure 108 on Plate IX. The swellings visible therein are of special interest, because very similar formations have been later seen by *Metchnikoff* (1888 *b*) with his *Pasteuria ramosa.* When *O. Israël* (1884) first succeeded in cultivating *Actinomyces hominis* on serum, he also obtained the characteristic club formation in vitro for the first time. The causative agent of the "farcin de boeuf" was named by its discoverer *Nocard* (1888) "bacille de farcin;" but already this first description leaves no doubt that this organism is a true Actinomyces. A special paper upon "The Morphology of Actinomyces," by *McFadyean* (1889), adds to the cocci, rods, threads and clubs already known, large circular bodies, which are believed to be related to the clubs. The latter were found to react differently when treated with Gram's method; and the cocci, too, were seen to be able to grow differently, viz., they either multiplied as such (in very young colonies) simulating strepto- and staphylococci, or they stretched themselves to rods and threads (in older colonies).

The very complete studies by *Bostroem* (1890) upon human actinomycosis brought much confirmation especially to the first findings of *J. Israël.* The clubs were seen to divide longitudinally as well as transversely, within the threads cocci, short and long rods were observed, and with young rods motility was ascertained. The pathogenic organism, isolated by *Eppinger* (1890) from a case of pseudo-tuberculosis and named by its discoverer *Cladothrix asteroides,* undoubtedly is also a true Actinomyces, though no clubs became visible. *Eppinger's* erroneous view concerning the mode of branching has been mentioned on p. 21. Coccoid as well as rod-like cells were found to be actively motile in young broth cultures. In old cultures the rods produced within the threads were seen to slip out, leaving the empty sheath behind. The thermophilic "Cladothrix," met by *Kedzior* (1896) in water, showed also true branching

and the characteristic powdery layer, so frequently produced by the Actinomycetes on solid substrates. Coccoid forms and young rods again exhibited motility. The same behavior was observed by *Rullmann* (1896, 1898 *a*) with his *Cladothrix odorifera* (i. e. *Actinomyces odorifer*), as well as with a yellow "Streptothrix," isolated from saliva. Another *Actinomyces* obtained by *Schürmayer* (1900) from tuberculous tissue, and described by him as "*Oospora* (*Streptothrix*) *proteus*" on account of its pleomorphism, grew temporarily in the form of motile cocci or motile rods. The cocci in this case again were able to multiply as such for some time, when kept at a low temperature. They then appeared like streptococci, but the tendency to produce branched compounds was much more pronounced than with genuine streptococci.

Feistmantel (1902) studied more closely the variable acid-fastness of "*Streptothrix farcinica*" and of other Actinomycetes. His results are very similar to those quoted above for *B. tuberculosis*. Full descriptions of the life history of *Eppinger's* organism, now correctly called *Actinomyces asteroides*, were published by *MacCallum* (1902) and by *Nakayama* (1906). According to *Doepke* (1902) different species may cause actinomycosis in man, some of them are aerob, some anaerob, clubs may be formed or may be absent, the coccoid forms may grow as such, or they may revert to rods and threads. Much variation in the formation of clubs and in their staining reaction has been also recorded by *Hollandt* (1906) and by *Loele* (1908). Gram staining and acid-fastness may even vary with the different parts of branched clubs. Occasionally threads were found by the first-named author up to 6μ broad, producing different kinds of gonidia, which fact was accepted as indicating a closer relationship between Actinomyces and Crenothrix. A detailed description of an *Actinomyces variabilis sp. n.* was given by *Th. Cohn* (1913). With the pleomorphism of the cells the formation of different colonies, was also studied in this case. Comparative tests of numerous Actinomycetes, contributing some additional details in regard to their pleomorphous character, have also been made by *Claypole* (1913) and by *Krainsky* (1914).

Among the so-called thread- or trichobacteria the old genus Leptothrix has been frequently mentioned as a prominent example of bacterial pleomorphism. However, the early observations of *Robin* (1871) and his contemporaries undoubtedly can not be accepted as sufficient proof in this respect, and several so-called Leptothrix species probably have been nothing else than a thread-like growth of other bacilli, principally of lactobacilli and of aerobic, as well as of anaerobic, spore-forming bacilli. *Leptothrix gigantea*, as described by *Miller* (1883), appears very similar to Crenothrix. The very different size of the threads, the slipping out of coccoid and of rod-like cells from the sheath, and their growing up, are the same in both cases. *Zopf* (1883) added to cocci, rods and threads, spiral forms as another type of growth of Leptothrix. With *Leptothrix buccalis* he ascertained later (1885) that the coccoid forms again may multiply as such for some time, before returning to the thread-like growth. The Leptothrix cultivated by *Dobrzyniecki* (1897) from the mouth, gave colonies similar to those of *B. anthracis*. One of the photographs accompanying the paper seems also to show some branching. *Vincentini* (1893), too, studied a so-called *Leptothrix. racemosa*, which, however, has been clearly a complex mixture of different organisms. *Beust* (1907) thought that *Bacillus buccalis maximus*, *Leptothrix maxima*, *Lept. innominata* and *Lept. racemosa* should be considered to represent merely stages in the life history of one organism.

Cladothrix dichotoma is characterized, according to *F. Cohn* (1875, p. 185), by its tendency to exhibit "false" branching only. But repeatedly the genus name has been erroneously used for naming species which belonged to the genus Actinomyces. *Zopf* (1881–1882) described as different types of growth of *Cladothrix dichotoma:* Cocci, rods, spirilla and threads; but his findings, though based on continuous miscroscopic observations, were strongly contested by *Winogradsky* (1888, p. 111). The results recorded by *Billet* (1890), however, are again in good agreement with those of *Zopf*, while *Büsgen* (1894) took his stand on *Winogradsky's* side. Spiral forms were not seen by him; small and large globular cells were discarded as "merely involution forms;" rods and threads alone were accepted as normal types of growth. *Migula* (1900, p. 39) published an interesting drawing (original fig. 45), which is reproduced as figure 39 on Plate K, presenting Cladothrix (*a–f*), as well as Actinomyces (*g–i*). Form and flagella-

tion of the motile cells are like those of *Azotobacter agile*, as seen by *Beijerinck* (1901 *b*). But while the picture given of "false" branching (*a*) is evidently a duplicate of that made by *Cohn*, the other figure (*e*), showing branched material grown on agar, seems to indicate, as far as can be seen from it, that also true branching may occur with this organism. The position of many of the branches, as sketched, is obviously not compatible with the assumption of "false" branching. If the growth which *Migula* had on his agar has really been that of Cladothrix it would demonstrate that under such conditions the resemblance between Cladothrix and Actinomyces (*e* and *h*) is indeed much greater than is generally believed. To *Migula* not only the cocci, but also the rods in old agar cultures are "merely involution forms." The frequently contested observations by *Zopf*, including those relating to the liberation of spirals with polar flagella from the Cladothrix threads, have been more recently confirmed by *Ellis* (1912) in his "Investigations into the Life History of *Cladothrix dichotoma* (Cohn)." He comes to the conclusion that Cladothrix is related on the one side to Crenothrix and Clonothrix, on the other to Pseudomonas and Spirillum.

Cocci, rods, threads, and spiral forms were also found by *Zopf* (1881–1883) with Beggiatoa. All short forms exhibited temporary motility. The coccoid cells either propagated as such, or they reverted into rods. *Engler* (1882) confirmed these results, but they were again utterly discredited by *Winogradsky* (1888). That, however, *Winogradsky's* statements can not be accepted as well founded, has been discussed (on p. 38). The answer given by *Zopf* (1895) deserves full attention, especially because new results are recorded therein, which confirm those obtained before. The findings of *Billet* (1890) were also in complete agreement with those of *Zopf*.

Crenothrix, too, can form, according to *Zopf* (1879), cocci, rods, and threads, and the cocci may either multiply as such or grow up to threads. Crenothrix is said to be unable to produce branches, *Schorler* (1904), however, who otherwise confirmed *Zopf's* results, also encountered a very similar, but branching, organism, which was made the type of the new genus Clonothrix. Only future experiments with pure cultures will make it possible to decide, whether this separation has been correct, or whether branching is equally common within this group as it is with all other bacteria.

3. CONCLUSIONS.

In regard to the occurrence of different cell forms within the various groups of bacteria the following conclusions can be drawn from the facts discussed on pp. 7–88:

(1) The monomorphistic theory of *F. Cohn*, *R. Koch*, and their followers, still accepted by many bacteriologists as being correct, is irreconcilable with numerous facts, which prove conclusively that all bacteria are pleomorphic. All well studied species—like *Micr. candicans*, *gonorrhoeae*, and *meningitidis; Strept. pyogenes*, *lanceolatus*, and *lactis; Bact. pestis*, *pneumoniae*, *radicicola*, *coli*, *acidophilum*, *bifidum*, *proteus*, *erysipelatos suum*, *pyocyaneum*, and *fluorescens; Bac. anthracis*, *subtilis*, *Azotobacter*, *Amylobacter*, and *Chauvoei; V. cholerae*, *Spirochaeta pallida; Corynebact. mallei* and *diphtheriae; Mycobact. leprae* and *tuberculosis*—have shown themselves to be able to grow in various, round, straight and curved, small and large, regular and irregular, cell forms. Budding, branching, and apical growth are common with all bacteria.

(2) That it was possible to uphold the monomorphistic theory for a considerable length of time, despite its erroneousness, is due to the following reasons:

(*a*) Differences in the cell form and in the appearance of the colonies have been usually accepted as a priori evidence of difference in species; and, therefore, most of the cultures exhibiting such differences, have been rejected as being contaminated.

(*b*) Genuine bacteria have often been laid aside as being no bacteria at all, because they showed budding, branching, or other peculiarities, which, according to the monomorphistic theory, should not occur with bacteria.

(*c*) In nearly all cases where undoubtedly pure cultures of true bacteria have exhibited various cell forms, only one of them has been accepted by the monomorphistic theory as "typical" or "legitimate," while the others were discarded, without adequate test, as being "atypical," "degenerate," or "involution forms."

(*d*) The cultural methods, as developed by the founders of the monomorphistic doctrine, make it often possible to keep a culture fairly constant for a considerable length of time, and to secure a continuous development of only one type of cells. Natural variations, as well as the different phases in the life cycles of the bacteria, are not easily noticeable under these conditions; but wherever they have been observed, the characteristic changes in cell morphology caused by them usually were again mistaken as growth of a "contaminating" organism or as some uninteresting "involution" form.

(3) In practically all cases where the so-called involution forms have been properly studied, it has been found that it was a mistake to classify them as such. This has been fully proved especially with *Micr. gonorrhoeae* and *meningitidis; Strept. pyogenes* and *lanceolatus; Bact. pestis, pneumoniae, radicicola, aceti, coli, typhi, proteus,* and *pyocyaneum; Bac. anthracis, mycoides, Azotobacter, Chauvoei,* and *tetani; V. cholerae, Spirochaeta pallida; Corynebact. mallei,* and *diphtheriae, Mycobact. leprae,* and *tuberculosis.* The endospores alone exhibit all marks of real involution. Many of the so-called involution forms, however, are most frequent when the bacterial development is at its height, part of them can be propagated as such, and later they are again replaced by the smaller cells of simpler morphology. The latter forms are generally best adapted to parasitic growth, though in the body, too, branching and otherwise "atypical" development is by no means absent.

(4) How far the alterations in morphological as well as in physiological behavior are due to variation and mutation among the bacteria can not be decided at present, because only insufficient information, or none at all, is available concerning the regular changes occurring in the different phases in the life cycles of the bacteria.

(5) The life cycles of probably all bacteria are composed of several subcycles exhibiting wide morphological and physiological differences. To secure all data pertaining to the life history of a species is much more difficult than to describe a bacterium in the ordinary manner. Long-continued investigations, made under different conditions, and controlled by a sufficient number of parallel tests, are indispensable in this case. Uniform cultural conditions and frequent transfers, made in regular intervals, tend to keep one type of growth constant; while successive transfers, made repeatedly during several weeks from and to various substrates, will always reveal more or less completely the pleomorphic character of every bacteria species. The best starting point for such experiments seems to be the symplastic stage, to be discussed in Chapter III.

(6) It is a grave, though often repeated, logical mistake to believe that the acknowledgment of the pleomorphism of the bacteria be equivalent to a negation of the existence and constancy of bacterial species. Just as all studies upon the pleomorphism of the fungi, algæ, and protozoa did not minimize, but have increased the accuracy in distinguishing between the various genera and species, so also systematic bacteriology will win considerably by every thorough investigation upon the life cycles of the different species. It is to be expected, and already clearly indicated by numerous well-confirmed results, that the old monomorphistic form genera and form species of *F. Cohn, R. Koch,* and of their followers will have to be thoroughly revised; and many of the so-called species, often described in the most superficial manner, will have to be canceled entirely as being merely fragments of the life cycles of other species. Only those species can be accepted as natural ones whose life history is fairly well known, and a correct systematic arrangement of the bacteria is not possible except upon such a natural basis.

(7) As far as can be concluded from the data available at the present time, it is probable that an increased knowledge of the life history of the bacteria will not lead to any change in the general position of the bacteria within the system. Their budding, branching, and apical growth may be considered as presenting additional evidence of their being related to the fungi, but it would not be justified to incorporate all bacteria on account of these characters among the fungi themselves, though this has been recommended by different authors. Other facts, especially with regard to the various modes of reproduction, undoubtedly strengthen the relations existing between bacteria and lower algæ, as well as between bacteria and protozoa. Many parallelisms are noticeable in the life histories of all these organisms; all of them are more or less pleomorphous.

II. REPRODUCTIVE ORGANS.

(GONIDIA. REGENERATIVE BODIES. SPORES. MICROCYSTS.)

1. GENERAL DISCUSSION.

In our first preliminary report (*Löhnis* and *Smith*, 1916 *a*, p. 700) we said concerning the reproductive organs:

All bacteria multiply not only by fission but also by the formation of "gonidia"; these usually become first regenerative bodies, or occasionally exospores. Sometimes the gonidia grow directly to full-sized cells.

The gonidia are either liberated by partial or complete dissolution of the cell wall, or they develop while still united with their mother cell. In the latter case the cell wall either remains intact or it is pierced by the growing gonidia, which become either buds or branches.

Some of the gonidia are filterable. They also produce new bacteria either directly or after having entered the symplastic stage.

The transformation of spore-free into spore-forming bacteria seems to be dependent on the conditions acting upon the symplasm and regenerative bodies.

The data collected on the foregoing pages will have shown that our observations concerning the pleomorphism exhibited by all bacteria in their vegetative stage, though at variance with the predominant monomorphistic doctrine, are amply confirmed by results obtained by many investigators, who in most cases have worked quite independently. In relation to the different modes and organs of reproduction of the bacteria the situation is very similar. If only the numerous findings to be quoted on the following pages would have met with adequate consideration, and if they had been brought into proper correlation, the doctrine still adhered to in most textbooks of bacteriology, that the endospores are the only special organs of reproduction of the bacteria, probably would never have been established.

As was said on p. 7, it is not always possible to reach a definite decision as to the vegetative or the reproductive character of certain cell forms described in the literature. Therefore, it will be necessary to refer occasionally back to one or the other item mentioned in Chapter I.

Before the special discussion of the character, the formation, and the development of the different reproductive organs is taken up, a brief historical resumé upon the discovery of the various modes of bacterial reproduction may be given first. In the second place the differentiation between reproductive organs and other cell products and artefacts must be considered. A few remarks upon some special problems (filterable vira, cell inclusions, aphanozoa, chlamydozoa, ultra-microorganisms, and heterogenesis), which become more easily accessible from our newly-won standpoint, will be added at the end.

(*a*) THE DISCOVERY OF THE DIFFERENT MODES OF REPRODUCTION.

When *E. Chr. Ehrenberg* in 1838 described the "infusoria" as "complete organisms," the genus Monas was reported as being able to produce "eggs," which in the case of *Monas Okenii* were seen to be liberated by the cells. With the small species of Monas, like *Monas termo*, as well as with spirilla and spirochaets, no analogous details could be made out. In the genus Vibrio, however, such granules were observed, as was also the case with the comparatively large Ophidomonas. In Gallionella a special organ, built up by four or more globoid bodies, was discovered, which the author considered as some kind of "ovarium."

Perty in 1852 was able to furnish much more information. Speaking upon protozoa, he says (p. 66 and 67):

Ich glaube nach zahlreichen Untersuchungen die Überzeugung hegen zu dürfen, dass eine gewisse Klasse von Bläschen und Körperchen, welche man in den Wimperinfusorien entstehen sieht, zur Fortpflanzung dienende, den Sporen vergleichbare Keime seien, für welche der Name Blastien (τὸ βλάστειον, Keim, Trieb) vorgeschlagen wird.

Die Fortpflanzung geschähe hiernach nicht durch gewöhnliche Substanzteilchen, wie *Dujardin*, noch Eier, wie *Ehrenberg* annimmt, sondern durch eigentümliche, im Innern der Tierchen entstehende, allmählich zahlreicher werdende Körperchen.

Concerning the Phytozoidia the following statement was made (p. 76):

Bei ihnen kommen auch die beiden Fortpflanzungsarten durch Teilung und durch Blastien vor; freilich ist man manchmal zweifelhaft, ob man Blastien oder nur den durch fortgesetzte Teilung in zahlreiche Parzellen zerfallenen Inhalt des mütterlichen Geschöpfes vor sich hat.

When discussing the monads (p. 83) the blastia are identified with *Ehrenberg's* "eggs"; the Vibrionida, too, are declared to grow up (p. 104):

. . . aus Anfängen, welche verschwindend klein sind.

The great difficulties arising from the minute size of these blastia and of the newly developed organisms are repeatedly pointed out, as for instance in the following sentence (p. 67):

Diese Kleinheit verhindert meist ihre Wahrnehmung, wenn sie zerstreut ausser dem Infusorienkörper vorkommen; aus gleichem Grunde kann man auch die Unterschiede der Anfänge vieler mikroskopischer Wesen nicht genau wahrnehmen.

Perty has been credited with the discovery of the bacterial endospores, and his drawings of "*Sporonema gracile,*" reproduced as figure 40 on Plate K (from original fig. XV, 26), prove that his observations have been very accurate in this respect. But evidently it has been overlooked so far that he also gave admirable pictures of the formation and development of what we now call gonidia. His drawings of spirilla, reproduced as figure 42 on Plate L (from original figs. XV, 28, 29B, and 31), deserve our full attention. The formation of the gonidia within the organisms and the upgrowth of the normal spirilla from minute beginnings are illustrated as clearly as in only very few pictures published in the modern literature. Concerning the large globular bodies, visible at some of the spirilla, *Perty* says (p. 132):

Brachte man ein Tröpfchen (of the culture) in einen Tropfen Brunnenwasser auf die Objectplatte, so bildete alsbald ein Teil der Spirillen durch Gerinnung Kugeln an sich, mit denen sie sich anormal bewegten, manche noch leicht, andere mühsam.

That is, a description of the so-called plasmoptysis has been given in this early work, more accurate than much of what has been written more recently upon this subject.

About the small and large "spores," i. e., micro- and macro-gonidia, of Gallionella ferruginea *Perty* made the following remark (p. 215):

Die kleinsten Körnchen zeigen oft Molecularbewegung; grössere bewegen sich wie Monaden scheinbar willkürlich. Sollen sie zu Fäden erwachsen, so bildet sich zuerst eine Hülle um sie, dann teilt sich der Inhalt und die Hülle verlängert sich.

Notwithstanding many inaccuracies to be found in *Ch. Robin's* "Histoire des végétaux parasites" (1853), the following references concerning his *Leptothrix buccalis* seem worth being quoted:

On peut quelquefois observer dans leur intérieur de très petits granules ronds, placés de distance en distance p. 347).

These round bodies were thought to slip out of the rods, to make part of the "granulations moléculaires" floating in the saliva, and eventually to develop to new threads (p. 351).

That *Hallier* (1865 *a*) and *Lüders* (1866) have dwelled upon the same subject has been also of no avail, though *Hallier* was right when he reported that the "granules" not always reproduce new threads immediately, but may for some time multiply as such, or may develop into larger round bodies, i. e., regenerative bodies. His favorite hypothesis, however, misled him to see "Penicillium spores" in them, which, of course, were also present in his very impure cultures, as were yeasts and all kinds of molds. To *Hallier* (1866–1896) all these various fungi were the result of the upgrowth of the bacteria and their granules, first called by him "micrococci" and later "plastids."

Karsten (1869) seems to have been the first author who used the term "micro-gonidia" for the small bodies, called blastia by *Perty*. Apparently he was influenced by the idea which he shared with *Hallier*, that bacteria and their "seed" were the offspring of vegetative and reproductive fungus cells; for the latter he used the term "Pilzgonidien."

Burdon-Sanderson (1871) saw "spheroids" (probably spores) elongate to rods, but he assumed also that bacteria might develop from "ultra-microscopic" bodies, not visible in

homogenous liquids. *Oertel* (1871) reports that in his diphtheria investigations he not only found cocci and rods, but also "Zellchen mit sprossendem Keimschlauch," which, according to his drawing, have been very similar to those observed by *Rindfleisch* (1872) and reproduced as figure 41 on Plate K (from original fig. 1 on Pl. XVIII). That these cells were not germinating spores has been made clear by Rindfleisch's statement that the "punctiform" bodies were actively motile, probably by one flagellum. He observed also for the first time that micrococci sometimes do not divide regularly, but increase in size, forming giant cocci, whose rôle will be discussed later.

When *F. Cohn* (1870) gave the complete description of *Crenothrix polyspora*, the formation of its motile "micro- and macro-gonidia" was also pictured. In figure 43 on Plate L two of his drawings (original figs. 11 and 13) are reproduced, one showing "ein Sporangium in der Mitte bandförmig verbreitert," the other a lateral club, filled with finely granulated protoplasm, considered by *Cohn* to have a spore-like character. To the same author (*Cohn*, 1872 *b*) we also owe the first fairly accurate investigation upon the bacterial spores, which was supplemented (1876) by *R. Koch's* study upon the spores of *B. anthracis*. As the bacterial gonidia are to many modern authors "merely fat," it is not uninteresting that *Koch* thought the spores were made up—

> . . . aus einem stark lichtbrechendem Tröpfchen, vielleicht einem Öl, welches von einer dünnen Protoplasmaschicht eingehüllt ist. Letztere ist die eigentliche entwicklungsfähige Zellsubstanz, während ersteres vielleicht einen bei der Keimung zu verbrauchenden Reservestoff bildet.

Much more important, however, is the fact that the very first photographs ever made of bacteria show in an excellent manner gonidia and regenerative bodies, i. e., those reproductive organs of the bacteria which, at the present time, are practically unknown to most bacteriologists. One of the pictures made by *R. Koch* (1877, original fig. 4 on Pl. XV) has been reproduced as figure 109 on Plate X. It shows, according to *Koch* (l. c., p. 423), "Bacillen mit mehreren seitlichen Sporen," and it is stated, in addition:

> Die Sporen . . . sind dicker als der Bacterienkörper und treten kugelartig aus diesem hervor.

The bacilli concerned are said to be related to *Bact. termo*, i. e., *Bact. fluorescens*.[1] Figure 110 is a reproduction of one of our own photographs (1916 *a*, fig. 40) showing formation of gonidia and regenerative bodies by *B. fluorescens*. *Koch's* picture was made with 500-, ours with 1,000-fold magnification; otherwise both are very much alike, and it is, indeed, surprising that this old observation neither has been followed up by *R. Koch* or by one of his pupils, nor has met with adequate attention elsewhere in the bacteriological literature. Another photograph by *R. Koch* (1877, fig. 5 on Pl. XVI), reproduced as figure 111 on Plate X, demonstrates the analogous stage in the development of *B. anthracis* (× 700). In this case, however, nothing has been said in the text concerning these round lateral and terminal buds and free round bodies, clearly visible in the picture. Again a comparison with a more recent photograph may be helpful. Figure 112 on Plate X is a reproduction from a picture made by *Günther* (1906, fig. 29, smear from the spleen of a mouse, × 1000), which presents the same type of gonidia and regenerative body, and also an interesting side branch above the latter; but again all is passed without any remark by the author.

Billroth (1874) was, like *Perty*, of the opinion that besides spores ("Dauersporen") small coccoid bodies are playing an important rôle in the multiplication of the bacteria. He states (on p. 16)—

> dass die zuerst in einer bacterienfreien Flüssigkeit sich bildenden Bakterien aus feinem und feinstem Coccos entstehen.

Concerning the formation and development of this "Coccos," we are told (pp. 21, 22):

> Eine weit häufigere und deutlicher zu verfolgende Umwandlung des Bakterienkörpers ist die zu kleinen runden Kügelchen, zu blassem Coccos.
>
> Der auf diese Weise in den Bacterien entstehende blasse Coccos vermehrt sich zuweilen gleich nach seiner Entstehung.

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[1] Some authors, like *Hauser* (1885) and *Pfeffer* (1888, p. 590) have been of the opinion that the old *Bact. termo* should be identified with *B. proteus*; *Beijerinck* (1897, p. 40) related it to *Bact. punctatum*, while *Macé* (1897, p. 913), *E. F. Smith* (1905, p. 170), and *Lehmann* and *Neumann* (1912, p. 411, footnote) define it as *Bact. fluorescens*. That this view is correct is evidenced by a remark made by *F. Cohn* (1872 *b*, p. 197) upon the green pigment produced by *B. termo*, and by a comparison of *R. Koch's* and our own photographs (figs. 109 and 110 on Pl. X).

Two of *Billroth's* drawings (original figs. 36 and 42), reproduced as figures 44 and 45 on Plate L, present several interesting details. Formation, multiplication, liberation, as well as upgrowth of the gonidia within the mother cell, are well discernible. The big inflations with their granules, usually discarded by later authors as "merely involution forms," make interesting counterparts to *Cohn's* Crenothrix "sporangium," shown in figure 43. It is especially noteworthy that the cells visible in figure 45, which are shedding their granules, were obtained from whey kept at 40–45 C., i. e., under conditions leading to an accumulation of lactobacilli, and just these organisms have furnished more recently excellent examples for this little known mode of reproduction. *Robin's* mixed species *Leptothrix buccalis*, mentioned above, probably also included some lactobacilli. *Billroth's* drawings should be further compared with those made by *E. Chr. Hansen* (1879) of acetic acid bacteria, which were reproduced as figure 15 on Plate E. The similarity of the reproductive organs produced by both groups of bacteria will be discussed on another page.

Bacterium putridinis, described by *Davaine* (1876, p. 23) as the cause of "une pourriture et ulcerations sèches" in plants, exhibited a very similar behavior. It is said to have presented itself in three different forms: "(1) en corpuscules amorphes, infiniment petits et innombrables, constituant un tourbillon mouvant dont la plupart des individues se perdent aux limites de la vision; (2) en filaments minces, courts, droits . . . atteignant au plus 0.005 mm. de longeur, . . . (3) en filaments generalement plus long . . . " And *Davaine* adds:

> Il est remarquable que les corpuscules les plus petits qui échappent presque à notre vue aient une vitalité supérieure à celles des bactéries bien développées. Ce sont sans doute . . . des germes.

The assumption that these germs might have been spores, on account of their "vitalité supérieure," would collide with the other fact mentioned before, viz., that "un tourbillon mouvant" was noticeable. That the resistance of the gonidia may be distinctly superior to that of the vegetative cells will be shown later.

In 1877 some good descriptions of the formation of gonidia by Cladothrix and Crenothrix were published by *Cienkowski*. He pointed out that it is often difficult to distinguish between gonidia and ordinary cell inclusions ("gewöhnliche Inhaltskörper"), and that the reproductive character of the former can be only ascertained by studying their further behavior and development. *Letzerich* (1878) saw that in blood taken from typhoid cases, isolated cocci grew up to large spheroids, called "Plasmakugeln," and that later new bacteria were formed within each of them. In 1878 *Ewart* recorded several equally interesting findings, secured by continuous observations of hanging drop preparations. With *Bact. termo* (1878 *a*) he found like *R. Koch* that bright, extremely small, almost spherical "spores" "escaped" from the cells, but he found in addition, that they were able to reproduce new rods. Not always, however, a direct upgrowth was observed; sometimes these "spores" first divided themselves into four "sporules," which multiplied as such for some time, but then gave again a new growth of rods. Analogous results were secured with Anthrax (*Ewart* 1878 *b*). Also in this case the "spores" either reproduced the bacilli directly, or at first "sporules" were formed, which grew as such for some time, before reassuming their regular function. That these so-called spores were no true endospores is proved, except by this behavior, by their not being heat resistant like genuine spores, according to *Ewart*, and by their taking the stain very easily, as was found out by *E. Klein*, who in 1883 made the same observations. The drawings made by the last-named author, which were reproduced as figure 21 on Pl. F, leave no doubt that these "spores" have been what we now call regenerative bodies and microcysts, which partially acted as gonidangia. *Perty's* discoveries upon the reproduction of spirilla have been confirmed by *Geddes* and *Ewart* (1878). Again the "spores" were seen to "escape" at the end or at the side of the cells. They were of unequal size, multiplied either as such, or grew up to new spirilla, and sometimes they were seen to be inclosed within larger spheres. Their multiplication took place by fission as well as by budding, inside as well as outside of the parent cells.

In the course of his investigations upon Actinomyces, *J. Israël* (1878) discovered that the "bright spores," formed in a lateral or in a terminal position by the threads, may multiply for some time as such before reproducing new rods and threads, and that the clubs, which

developed at the end of the threads, may either break up and liberate their granular content, or may produce "blasse Körnchenhaufen" by fission or by budding.

Van Tieghem (1879 *a* and *b*) studied carefully formation and germination of so-called spores of *Spirillum amyliferum*, of a vibrio, and of a spirochaete found in oysters. Unfortunately, their resistance against drying and heating has not been examined. In accordance with results obtained by *Heydenreich*, *Guttmann* (1880) ascertained that also Spirochaeta Obermeieri produces "spores," which occurred singly or in pairs, were actively motile, but could not be seen to grow up to new spiral forms. Similar motile "granules" were noticed by the last-named author in the blood of patients afflicted with pneumonia crouposa, scarlatina, typhus abdominalis, typhus exanthematicus, diphtheria, and erysipelas. Special attention was paid to their differentiation from other blood granules. More data relating to Spirochaeta Obermeieri were furnished by *Albrecht* (1881), who found nothing but granules in the blood during the intermittent stage, while during the attack all forms, from granules up to full grown spirochaets, became visible. He called the motile granules germs ("Keime").

Formation, multiplication and germination of the gonidia produced by the large trichobacteria (Crenothrix, Cladothrix, Leptothrix, Beggiatoa) have become well known by the studies made by *Zopf* (1879–1885). Figure 47 on Plate M is a reproduction of his drawings of Crenothrix Kühniana (1883, original fig. 6), figure 48 one of Beggiatoa alba (1883, original fig. 27).

Engler (1882) confirmed *Zopf's* findings and added a new form, *Phragmidiothrix multiseptata*. The picture he made from it has been reproduced as figure 46 on Plate L (from original fig. 24). It is of special interest because of the small branches, apparently produced by gonidia germinating within the sheath. However, no final evidence could be secured in this respect.

Unfortunately, the results obtained with these comparatively large organisms have not been used as a help for testing the smaller bacteria along similar lines. The trichobacteria were either declared not to be bacteria at all, or they were removed to a special position as "higher" bacteria (see p. 22). But all recent, as well as many of the earlier, observations prove conclusively that formation and development of the gonidia are very much alike with all—"higher" and "lower"—bacteria.

Another opportunity to become acquainted with gonidia and regenerative bodies was given to *R. Koch* (1881) when he made the two photographs reproduced as figures 113 and 114 on Plate X, showing anthrax and oedema bacilli in the tissue accompanied by globular forms. However, again, as in 1877, no attention whatever was paid to these forms, which fact is especially surprising, because at that time *Koch's* standpoint concerning the etiological significance of the anthrax bacilli was strongly contested by *Fokker* (1881–82), who pointed out that in numerous cases no bacilli but only small coccoid bodies had been found, and that the latter probably were produced by the former and reproduced them in their turn. More evidence was furnished in this direction by *Archangelski* (1883), *Roloff* (1883), and *Toussaint*. According to a communication made by the last-named author to *Magnin* (1884, p. 150), he noticed, like *Ewart* and *E. Klein*, that the anthrax bacillus is able to produce smaller and larger spherical or elliptical "sporangia," especially when kept in blood at 37–40° C. Three to six "spores" were seen to escape from each "sporangium," and a new development of rods from these "spores" was also directly observed by *Toussaint* in *Ranvier's* chamber.

In regard to the bacillus of symptomatic anthrax *Ehlers* (1884) came to similar conclusions; he says:

> Der Rauschbrandpilz bildet zwei getrennte Entwicklungscyklen, welche entweder in der Sporen- oder in der Coccen-Gonidienbildung ihren Abschluss finden.

These "cocco-gonidia" were also found to be able to reproduce typical symptomatic anthrax in the animal.

However, all these findings were discarded by the *R. Koch* school of bacteriologists. *Loeffler* (1887, p. 171) declared that *Fokker*, *Archangelski*, *Roloff*, et al. had been "wrong without exception," though he does not furnish any evidence supporting his statement. The absurd dictum made by *Fraenkel* in regard to the "unnecessary" and "illegitimate" nature of the cocooid reproductive organs of *B. anthracis* was quoted on p. 27. *Ehler's* results were dis-

credited by *Kitt* (1887), but later confirmed by *Grassberger* and *Schattenfroh* (1907). The interesting manner in which *Hibler* (1908) tried to get rid of the embarrassing presence of the large round forms (regenerative bodies or gonidangia) of *B. Chauvoei* has been mentioned on p. 67. Figures 115 and 116 on Plate X are reproductions of two others of his protographs (original figs. 17 and 18, Pl. VIII, ×2,000), which demonstrate clearly that with this species it is not so easily possible to overlook these "illegitimate" formations, as *R. Koch* and his followers could do with *B. anthracis* and the smaller bacteria. The convenient "explanation," that they are "merely inflations" or "simply involution forms," has, of course, proved helpful here as in many similar cases.

On the other hand, *R. Koch* (1882–1884 *a*) and several of his pupils did not hesitate to ascribe "spores" to tubercle, typhoid, and other bacilli, usually on account of no other reason than that these bacilli sometimes show inclusions, which are not stained by aqueous dyes, and that their resistance against drying may be sometimes rather high. *Koch* declared that the tubercle bacilli produce spores "like the anthrax bacilli," though he usually saw 4–6 unstained inclusions in each tubercle bacillus. And he also asserted that occasionally these not stainable "spores" alone were present within the tissue:

> Ihre Anwesenheit verrät sich nach dem Verschwinden der Bacillen nur durch die infectiösen Eigenschaften der käsigen Substanz, in welche sie eingebettet sind.

He also noticed that in some preparations only stained granules became visible instead of the bacilli, but there was no doubt to him that these were "granules of plasma cells." However, *Klebs* (1883 *a* and *b*), *Babes* (1883), *Malassez* and *Vignal* (1883–1884), *Biedert* and *Sigel* (1884), *Artigalas* (1885), *E. Klein* (1885), *Amrusch* (1886), and *Lutz* (1886) furnished soon a large amount of evidence that these stainable granules may be, and often are, the true offspring of the bacilli, and that they are able to reproduce the long forms.

The typhoid "spores" observed by *Eberth* (1880) and *Gaffky* (1884) have been refuted by *Buchner* (1888) and by *Pfuhl* (1888). Similar claims made by *Hueppe* (1884) concerning *B. acidi lactici* and *B. cyanogenes* were retracted by his pupil *Epstein* (1890). What *A. Neisser* (1881) and *G. A. Hansen* (1882) declared to be lepra "spores" have been undoubtedly regenerative bodies, as is to be seen especially from the description given by *Neisser*. The results of the leprosy studies of *Babes* (1883), *Lutz* (1886), and *Bordoni-Uffreduzzi* (1888 *a*) fully confirm this conclusion.

The florid hypotheses, developed by *Béchamp* (1883) in his book on "Microzymas" in relation to the bacteria and their various reproductive organs, have been distinctly unfavorable to further studies upon these problems; and the usage established by *Zopf* (1883) to take the term "cocci" as practically equivalent to "gonidia," has also caused considerable misunderstanding. *Hueppe* (1886, pp. 109, 125) blamed *Zopf* for this incorrect denomination; not every globular or ovoid body should be called coccus, and this name should never be used for reproductive organs. But *Hueppe* also emphasizes on the other hand (l. c., p. 133) that globular bodies which are able to multiply as such should be called cocci, not gonidia. So again *Zopf* would have been correct, because all gonidia undoubtedly can multiply as such by fission, as well as by budding, and often do so before reproducing the larger cells.

In his "Traité de Botanique" *Van Tieghem* (1884, p. 1105) introduced the name "cyst" as designating those resting cells, which later have been also called "arthrospores." He defines them as follows:

> Les kystes ne sont que des cellules ordinaires . . . qui grandissent, changent de couleur, épaissent leur membrane et passent enfin à l'état de la vie latente. À la germination, le corps protoplasmique du kyste, revêtu de la couche interne de la membrane, reprend sa couleur primitive, se cloisonne dans la même direction que lorsqu'il faisait partie de filament, déchive la couche externe cutinisée de la membrane et s'allonge au dehors.

The exact meaning of the term "arthrospore," introduced into bacteriology by *DeBary* (1884), has been given neither by him nor by *Hueppe* (1886), who made it popular. The latter author only points out that arthrospores are always of globular form and do not multiply as such. That he also recommended to include the gonidia among the arthrospores (l. c., p. 128) was an evident mistake.

Arthrospores were especially attributed by *Hueppe* (1885) to the cholera bacilli. His drawings, reproduced as figure 49 on Plate M (from original fig. 2), leave no doubt that he saw those reproductive organs, which we now call regenerative bodies. Germination by stretching was repeatedly observed; in one case formation, as well as germination, of this organ was continuously studied with the same cell. Increased resistance of these bodies, when dried, was also noticed. *Kitasato* (1889) was unable to confirm *Hueppe's* findings, and this negative result has been often quoted in the textbooks (e. g., by *Pfeiffer* 1896, p. 536; *Heim*, 1906, p. 187; *Lehmann* and *Neumann*, 1912, p. 517) as being full proof of the inaccuracy of *Hueppe's* work; but it has not been quoted, on the other hand, that there are recorded many more positive results, all confirming and extending *Hueppe's* discovery. *Babes* (1889) saw that terminal round bodies are produced by the cholera vibrio, which after separation grew up to new bacilli; within long spirilla he found several of such round bodies. Their higher resistance against drying was carefully tested by *Finkler* and *Prior* (1885), as well as by *Firtsch* (1888), with *V. proteus*, by *Weibel* (1888) with *V. lingualis* and *saprophiles*, and by *Esmarch* (1887) with his *Spirillum rubrum*, where the granules, as their author says, "are arranged like the peas in an opened pod." *Sorokin* (1887–1890) called these bodies "spores," though they did not stand the heating, but he saw them germinate while still within the parent cell, which process led to those interesting branched forms reproduced in figure 29 on Plate H, and induced him to call his organism *Spirillum endoparagogicum*.

Development of new cells from the gonidia, still inclosed in the old cell, has also been described and drawn by *Künstler* (1884) for his *Bacterioidomonas sporifera*. Nearly 20 years later the same occurrence was studied by *Chatton* and *Pérard* (1913). Their drawing, reproduced as figure 50 on Plate M (from original fig. on p. 1233), leaves no doubt that their *Metabacterium polyspora* is identical with *Künstler's* organism, whose existence was evidently unknown to them. Like *Künstler* they call the 1–8 new rods which were seen to develop from "masses chromatiques," "spores," obviously an erroneous interpretation.

Analogous endogenous upgrowth of the gonidia was discovered by *Finkler* and *Prior* (1884–1885) with their vibrio. They either saw the motile "spores" coming out of the mother cells and developing outside into new vibrios, or the "spores" remained and grew inside of the old cells, which increased in size and often assumed a club-shaped appearance. Later these "nurses" (Ammen), as the authors call them, broke up and set the new bacilli free. *Ferrán* (1885) described large round or mulberry-like bodies of the cholera vibrio, which grew up from the granules contained in the thread-like cells, and which either send out thin threads becoming new spirilla or produced new spirilla inside of their cell walls, which later dissolved. The Spanish author indicates in addition that similar modes of reproduction probably occur with cocci and bacilli, too, and he mentions a Dr. *Colvée* in Valencia who observed similar things with the tubercle bacillus. In another paper by *Künstler* (1885) "De la position systématique des bactériacées" the following important statements have been made concerning spore forming bacilli and spirilla:

> D'après certaines découvertes récentes il semblerait que ces formes se transforment souvent en vésicules claires, de dimensions considérables rélativement à leur taille primitive. Dans ces vésicules se produisent une foule de spores, analogues à des micrococques, qui sont mises en liberté par la déhiscence des parois.
>
> Les spores des Spirilles se divisent au sein de leur enveloppe et finissent par acquérir alors la faculté de se mouvoir. Ce n'est qu'ultérieurement que les sporules deviennent libres et germent.

In the same paper a spirochaete-like organism has been described under the name *Proteromonas Regnardi*, which was placed between bacteria and flagellates, and which was found to produce an inflation at or near the middle of the body, from which small "buds" were seen to separate, which became motile and grew up to new individual cells of "Proteromonas."

The picture reproduced as figure 122 on Plate X from *Artigalas'* "Microbes pathogènes" (1885, original fig. 1 on Pl. 5) shows the giant cells formed by Pneumococcus, which the author calls "spores," producing and liberating "sporules." *Maddox* (1885) published at the same time a similar drawing of inflated, club-shaped cells of *Bacterium lactis* (i. e., *Streptococcus lactis*), which let out their deeply staining granular content, and which were accepted by the author as "sporangia," not as "degenerate" cells.

Evidently without knowledge of the work done in France, in England, and in Spain, *Schroen* (1886–1891) in Italy found out that the tubercle bacillus may produce globular "spores," which eventually increase in size and produce internally several "daughter spores," which later leave the cyst ("Kapsel") singly or in chains, forming again new granulated bacilli. With numerous other species (*B. anthracis, Megaterium, V. cholerae,* etc.) he secured analogous results. The content of the large inflated cells, the "involution forms" of the German authors, was seen to transform itself into small coccoid and rod-like bodies, which later were liberated. In a footnote to an abstract of *Schroen's* first paper, *Baumgarten* in his "Jahresbericht" (1886) strongly doubts the accuracy of this work and mentions as foremost reason for this that neither *R. Koch* nor he himself had ever noticed such modes of reproduction.

Klebs (1887, p. 76) was of the opinion that in many cases the deeply staining granules ("chromatophilen Körner") visible in the cells, which he named "microsomes," may serve as starting points for new bacterial development. *Hauser* (1885) noticed that the so-called involution forms of his *Proteus vulgaris*, whose interesting photograph is reproduced as figure 120 on Plate X (from original fig. 16 on Pl. X) often contained one or more small, dark granules, or, more frequently, a globular, bright body, whose nature remained problematical to the author. All these large, globular, pear- or dumb-bell shaped forms were actively motile, reproduced quickly (within 12 hours) luxurious colonies, could be made constant in their characteristic appearance, and proved to be fairly resistant against drying, i. e., they exhibited in no way any sign of "involution," but presented themselves as an interesting connecting link between rudimentary gonidangia and sporogeneous cells. The lateral bud attached to the long rod at the right side of the picture and the many small forms apparently growing up from the gonidal stage are equally noteworthy.

The organism described by *Bordoni-Uffreduzzi* (1888 *b*) under the name *Proteus hominis capsulatus*, which, however, undoubtedly is to be placed in the neighborhood of *B. pneumoniae*, produced within the body rods and large numbers of gonidia, as may be seen from the liver cut, reproduced as figure 123 on Plate X (from original fig. 6 on Pl. VIII); in the cultures also large globules were found, which reproduced rods, and many other irregular forms, mentioned already on page 55.

Of special interest is a report made by *A. Neisser* (1888) upon "spore" formation of *B. xerosis*. The bodies concerned, for which the special treatment, known as *Neisser's* spore-staining method, had been developed, are those granules or disks in the so-called barred type of the diphtheria group, which are now called gonidia, while *Neisser* used this term for the whole, club-like structure. The most important findings were these:

Jedes einzelne Teilglied wächst wieder zu einem neuen Bacillus aus. Die Wachstumsrichtung dieser Teilchen steht aber senkrecht auf derjenigen, in welcher sich der einzelne Bacillus zu der keulenförmigen . . . Kette ausbildete.

This mode of development leads to the parallel arrangement of short rods of uniform length, so characteristic for this group. Bacilli containing 3 or 4 granules, "welche als erste Anfänge der Bacillen ganz kurze Ansatzstücke zeigen," were also present. And it was further emphasized that these "spores" are produced in greatest numbers when the development reaches its maximum, not when it comes to its end, as with *B. anthracis*.

All these observations are in good agreement with some of our recent findings concerning the development of the gonidia of *B. azotobacter* and of other species. Still more complete, however, is the coincidence of facts incorporated by *Tomaschek* (1888) in the drawings of his large *B. muralis*, reproduced as figure 51 on Plate N (from original fig. on p. 183), and those secured in our Azotobacter studies. In fact, every detail visible in this picture could be accepted as representing some stage in the development of *B. azotobacter*. The large ovals surrounded by concentric slimy layers, the formation of the small globular gonidia, their liberation, as well as their upgrowth inside of the mother cell, are all as with Azotobacter. *Hansgirg* (1889) vigorously maintained against *Tomaschek* that this so-called *B. muralis* be no bacillus at all, but a colorless alga. That again is exactly what has been asserted by several authors in

regard to the large cells of Azotobacter, though our more recent findings leave no doubt that they are merely a type of growth in the life cycle of spore-forming bacilli of the Subtilis-Mesentericus group.

Another interesting picture of the formation of gonidia within a bacillus has been published by *W. Miller* (1889, p. 54), when he described what he wrongly called *Jodococcus vaginatus*. A glance at figure 52 on Plate N (reproduced from original fig. 15) shows that it makes a good counterpart to some of the older drawings made by *Billroth* (see fig. 44 on Pl. L) and by others of the trichobacteria, and that *Baumgartner* (1909) was perfectly right when he removed this organism as *Bacterium iogenum* to its proper place.

What *Beijerinck* (1888), *Frank* (1890), and *Prazmowski* (1890) described as liberation of "swarming bodies" ("Schwärmer") by *B. radicicola* is, at least partially, to be classed among the early observations upon bacterial gonidia. The last-named author compared them to small bright globular spores ("Sporenkügelchen"); *Atkinson* (1893) called them zoospores.

Dowdeswell's investigations (1889–1890) upon the cholera organism brought much confirmation to those of *E. Klein*, *Ferrán*, and *Schroen*. "Sporangia" producing "sporules," rods, and threads splitting up into granules, and the regeneration of normal forms from these sporules were once more studied continuously with the living material. The drawing of a stained preparate of cholera, published by *Cornil* and *Babes* (1890, original fig. 275) and reproduced as figure 124 on Plate X, may be compared with *Hueppe's* sketches, reproduced as figure 49 on Plate M. An analogous picture of the first-named authors, showing gonidia and regenerative bodies of the tubercle bacillus, was reproduced as figure 102 on Plate IX.

MacFadyean (1889) noticed similar large globular bodies with Actinomyces and thought they were related to the clubs, while the smaller "cocci" were declared by him to be the "seed" for new development in the animal. *Bostroem* (1890) called the bright, darkly staining, pear-like granules which he found in and outside of the Actinomyces threads "spores." Within the clubs he also observed such granulated threads, which were seen later to disintegrate, liberating the "spores." That they may cause budding and branching was found out by *Eppinger* (1890), who noticed that the granule visible in the thread at first develops a small "wart," which then grows out into a branch, just as had been seen by *Sorokin* with his *Spirillum endoparagogicum*. The interesting forms of "*Streptothrix cuniculi*" photographed by *Schmorl* (1891) were reproduced as figures 89 and 90 on Plate VIII. The granules within the threads, but also their liberation are well discernible, especially their coming out of one of the inflations visible in figure 90; lateral buds and the beginning of branching are equally conspicuous. *Mafucci* (1892) recorded similar findings with the avian type of *B. tuberculosis*, and *Fr. Fischel* (1893) reported concerning the human type of this organism:

> In manchen der klöppelartigen Verdickungen sieht man beiläufig in der Mitte derselben äusserst kleine, hellglänzende, runde oder ovale, an sehr verkleinerte Milzbrandsporen erinnernde Gebilde.

Marpmann (1893) found in sweepings from the street round spore-like germs of the tubercle bacillus, which gave him normal cultures after having been kept for one hour in the steam. *Coppen-Jones* (1895) recommended to place the "spores" of the tubercle organism next to the chlamydospores of Mucor and similar fungi. *Semmer* (1895) met again the bright granules in the threads, as well as in the big inflations, of tubercle and glanders bacilli, and saw them when liberated grow up to new rods and threads. And the observations made by *A. Neisser* (1888) with *B. xerosis* were confirmed and extended by *Escherich* (1894) in his work upon the diphtheria bacillus.

A permanent loss of endospore formation was first recorded by *Lehmann* (1888) with *B. anthracis*. The "microspores," which were found in such asporogenous rods, were killed when kept 2–3 hours at 60° C. *Roux* (1890) collected additional experimental evidence upon the same subject, while *Novy* (1894) noticed with an asporogenous strain of *B. oedematis maligni* that moderate heating (1 hour at 58° C.) had no deleterious effect, thereby proving beyond doubt that the easily stainable granules, which were present in and outside of the rods, were more resistant than the vegetative cells and able to act as reproductive organs. The subsidiary rôle played by the "granules" in such cases was already indicated to some extent by analogous

findings with *B. anthracis* and *Megaterium*, made by *DeBary* (1884). *Weibel* (1888), on the other hand, found once more large globular bodies and big club-like inflations within the threads of an asporogenous culture of *B. anthracis*, and *L. Klein* (1889) reported that he obtained, as a "contamination" from a culture of *B. Megaterium* a spore-free "new" *B. allantoides*, which produced large "sausage-shaped" accumulations of "cocci", probably similar to those seen by *Billroth* (1874) and reproduced in figure 44 on Plate N.

A photograph published in the "Atlas" of *Fraenkel* and *Pfeiffer* (1895) of what the authors call "crippled degeneration forms" of *B. Chauvoei*, widely differing from the typical "vorschriftsmässigen" cells, has been reproduced as figure 117 on Plate X (from original fig. 60 on Pl. XXX). It makes an excellent object for comparison with the analogous "involution forms" in *Hauser's* Proteus picture (fig. 120). Rudimentary spore formation is well noticeable in both. In addition, the three figures, Nos. 118, 119, and 121, are equally worth studying. They were reproduced from *Maassen's* (1904) paper on the "involution forms" of the bacteria (original figs. 4 and 7 on Pl. X, and fig. 1 on Pl. XI, respectively), and demonstrate the development of *B. pestis*, *B. lactis aerogenes*, and of *V. cholerae* on lithium chloride agar. The same hardened granules appear in the inflated globular and club-shaped cells. A picture of *B. pyocyaneus*, from salt agar, made by *Matzuschita* (1900) and reproduced as figure 125 on Plate X (from original fig. 26), illustrates the same fact, in reference to which *A. Fischer* has made an interesting hypothetical remark already in 1891, which, however, has never been tried experimentally. It is very probable, indeed, that *A. Fischer* was right when he assumed that by an increase in salt content of the substrate perhaps many bacteria could be induced to form spores, which otherwise are not so inclined. According to our experiments the spores are closely related to the regenerative bodies, and the formation of these reproductive organs is greatly favored by drying. A higher salt concentration in the agar causes the analogous osmotic effect, and it is, therefore, easy to understand why practically all the pictures made by *Matzuschita* and *Maassen* from their salty cultures show various phases in the development of regenerative bodies and gonidangia. The figures 5, 6, 18, 36, 46, 57, 84, 118, 119, 121 and 125 on Plates I–V, VII, and X, which were made from their photographs, are by no means pictures of some quaint and unimportant "teratologic" type of growth, as *Maassen* assumed; in fact, they all illustrate interesting phases in the formation and development of the reproductive organs, as characteristic of the various species.

The same holds true concerning other so-called involution forms, mostly from old agar cultures, shown in the photographic atlasses of *Fraenkel* and *Pfeiffer* (1895) and of *Itzerott* and *Niemann* (1895), some of which have been reproduced as figures 25, 30, 47, 79, and 80 on Plates III, IV, and VII. Others are copied as figures 126–130 on Plates X and XI (from original figs. 7, 16, 46, 60, and 104 in the atlas of the last-named authors) illustrating analogous stages in the development of various spirilla (126), *B. anthracis* (127), *B. capsulatus Pfeiffer* (128), *Vibrio Bonhoff* (129), and *Spirillum rubrum* (130). The characteristic budding of the globular darkly stained bodies is clearly visible in all of them.

Other exceptionally good photographs of regenerative bodies, budding out in a lateral position, were made in 1891 by *Zettnow;* one of them is reproduced as figure 131 on Plate XI (from original fig. 14). But they, too, were discarded as being probably "merely involution forms." Further studies made with impure cultures of *Spirillum Undula* (*Zettnow*, 1896) furnished among others the interesting picture reproduced as figure 132 on Plate XI (from original fig. 16). Round darkly stained and also not stained globular bodies are visible inside, as well as outside, of the spirilla; some of them seem to sprout sideways, and a contaminating rod exhibits also its typical lateral buds. *Zettnow*, however, did not pay any attention to the last-named fact, and the globules of the spirilla are to him simply "vacuoles," though vacuoles of a truly astonishing behavior. *Zettnow* informs us that these "vacuoles" transformed themselves into "globules" of various size, which separated themselves from the parent cell and became free.[1] After having liberated themselves these transformed "vacuoles" exhibited another equally

[1] He says literally, that "die Hohlräume sich in kleinere und grössere Kugeln umwandeln, diese sich abtrennen und schliesslich frei werden."

surprising feature, viz., they were now difficult to stain, and only after having been treated with a mordant ("Loeffler's Beize") they took the stain at least at the outside. Because as *Zettnow* states (contrary to the facts mentioned above) nobody had ever spoken of spores in connection with spirilla; he thinks that he is justified to class these vacuole-globules as signs of degeneration. In another paper (*Zettnow*, 1897) he returns to the subject, after having now worked with pure cultures, which were studied living, stained with methylene blue. Spirilla containing granules were especially actively motile; nevertheless the granules are to *Zettnow* still the mark of degeneration. They are declared now to have been gas bubbles, which persist and agglomerate after the spirilla have died. They gave "fat reaction," too, though they were easily stained by methylene blue; and because they also appeared as "Chromatinmassen," the author is inclined to think—

dass sie bestimmt sind, die Art über die ungünstige Zeit, in welcher die Vermehrung stockt, zu erhalten.

Buds, however, are still to him "krankhafte Degenerationsformen." *Kutscher* (1895 *a*), who had isolated the pure cultures used in these studies, obtained analogous results. He also saw the bright granules within the spirilla and the same characteristically branched forms, as described and drawn by *Sorokin* (see pp. 72 and 96), but because the granules did not show a high resistance against heating, and germination tests apparently were thought to be superfluous, they were declared to be no spores. *Cunningham* (1897), on the other hand, noticed once more that cholera spirilla may be reproduced by coccoid forms. *Kohlbrugge* (1900–1901) recorded analogous results with several water vibrios, and *Nakanishi* (1900) with *V. cholerae*, *V. Finkler-Prior*, and *V. Metchnikovii*. In the latter case the globular bodies were found to predominate in 4-day-old cultures, and after being transferred to new substrates they germinated readily to new vibrios. *Migula* (1897, Vol. I, p. 157), however, was of the opinion that the round bodies, which *Perty* had found with the spirilla, had been—

. . . andere Organismen, da sie teils endständige, von dem Spirillum durch eine Scheidewand deutlich getrennte, teils irgendwo dem Rücken aufsitzende, keinerlei genetischen Zusammenhang mit dem Spirillum bekundende Kugeln sind.

Undoubtedly, *Migula* had not read the careful description given by *Perty*, quoted on page 91, otherwise he would not have made such an incorrect statement. Furthermore, it is not without interest, that he himself (*Migula*, 1904) published a photograph of some spirilla, reproduced as figure 133 on Plate XI (from original fig. 8 on Pl. II), showing exactly the same body, or "foreign organism" according to his opinion, attached to the "back" of one of the spirilla in his own preparate. This picture should also be compared with figure 130 (*Spir. rubrum*, photographed by *Itzerott* and *Niemann*). Another photograph given by *Migula* (1904) on the same plate, has been reproduced as figure 134 on Plate XI. It was destined to illustrate the flagellation of *B. proteus*, but it exhibits in addition the round bodies characteristic of this species. How little *Migula* knew, indeed, of the reproductive processes common among the bacteria, and about the literature covering this subject, is very clearly indicated by the manner, in which he refutes in the last-named publication (1904, p. 61) some observations made by *Trambusti* and *Galeotti* (1892) concerning the formation and liberation of gonidia, though they were in complete accordance with the earlier findings of *Perty, Billroth, Ewart, Toussaint, Künstler, Finkler* and *Prior, Ferrán, Artigalas, Maddox, Schroen, Tomaschek, Dowdeswell,* and others cited above. To *Migula* such an occurrence is simply impossible:

Ein solcher Vorgang kommt bei den Bakterien der ganzen Art und Weise ihrer vegetativen Entwicklung nach nicht vor.

In figure 53 on Plate N another example of this "impossible" mode of reproduction is shown, as it was drawn by *Babes* (1895, original fig. 13 B) when he studied Ascobacterium luteum. Formation, multiplication, and upgrowth, as well as liberation, of gonidia and young rods are all well visible.

More evidence concerning the occurrence of globular reproductive organs with various nonspore-forming bacteria, especially with *B. typhi, dysenteriae* and *V. cholerae*, was furnished in a series of important contributions by *E. Almquist* (1893–1917), who especially emphasized,

that if we keep the bacteria in the laboratory under conditions more similar to their natural environment, they will reveal at once much more of their life history than they are able to exhibit under the monotonous artificial conditions under which they are usually compelled to live. At first it was shown (*Almquist*, 1893) that *B. coli*, as well as *B. typhi*, when grown at a low temperature (10–11° C.) in manure soil, produce by fragmentation, as well as by budding, very small round bodies, which transferred to new substrate (broth) at room temperature quickly reproduce new normal, often also curved, rods. Further studies (*Almquist*, 1904) added to the small ones larger round bodies, which were called "conidia" by the Swedish author, and which were also found to bud out at the side or at the end of the vegetative cells, often supported by a short stem. They were discovered in both cholera and typhoid cultures, especially when 2–3 per cent NaCl had been added to the substrates. They were easily stainable and reproduced readily on new substrates each one or two small, very motile, young vegetative cells. With cholera the germinating rod looked at first very much like typhoid, while in the latter case the first generation was extremely thin ("nadelartig"). It was noticed, too, that these "conidia" are able to multiply as such by budding. All these findings were confirmed and extended in the publications of 1906–1908; they are mostly based on direct observations of the living material. In the 1907 paper *Almquist* compares his conidia with the reproductive organs of the iron bacteria, also called by him "conidia." Some drawings published in 1908 are reproduced as figure 54 on Plate N (from original figs. 5, 13, and 21). It must be admitted that they are not very impressive, but everybody who has had some experience in this direction will acknowledge their accuracy. But it was not until 1916 and 1917 that good photographs were also furnished by *Almquist*. Five of them are reproduced as figures 135–139 on Plate XI (from original figs. 4, 5, and 23 in the 1916 and figs. 1 and 4 in the 1917 papers), illustrating formation and development of the "conidia" of *B. typhi* (figs. 135, 136, and 138), *B. dysenteriae* (fig. 137), and *V. cholerae* (fig. 139). Besides these species, *B. diphtheriae*, *B. acidi propionici c*, several micrococci and coli-like organisms were also studied. A considerable number of the experiments was made with single-cell cultures; dried agar kept at 10–14° C. proved to be especially favorable for stimulating the development of these round reproductive forms. It is obvious that *Almquist's* discoveries are in complete agreement with many earlier, as well as with more recent, observations made along similar lines; but probably nobody has followed so patiently and extensively the formation, multiplication, and germination of what we now call gonidia and regenerative bodies, as *Almquist* did.

That his findings were contested by authors like *Gotschlich* (1909) and *Kruse* (1910, pp. 8 and 31) is not surprising, but does certainly not reduce their great value to any extent. On the other hand, it is again rather interesting to compare these pictures of *Almquist* with some others contained in various papers and textbooks, which reveal the same details, though as a rule, this was not noticed or at least not mentioned, by the respective authors themselves. Figure 140 on Plate XI is a reproduction of a photograph made by *Friedrich* (1892, original fig. 4 on Pl. V) from a 4-day-old cholera culture. Figure 141 is the picture of a young Pyocyaneus culture, published by *Muir* and *Ritchie* (1903, original fig. 69); it should be compared with figure 31 on Plate III, showing the same process, i. e., germination of gonidia and of regenerative bodies, with the plague bacillus, photographed by the same authors, and with figure 136 on Plate XI (germinating gonidia and regenerative bodies of *B. typhi*, *Almquist*). Figure 142 was made from *Günther's* textbook (1906, original fig. 54), presenting the development of regenerative bodies of *B. enteritidis*. Figure 143 illustrates the same process with *B. ochraceus* as photographed by *Migula* (1900, Vol. II, Pl. XI, fig. 3), and as figure 144 another picture made by the same author (*Migula*, 1900, Vol. II, Pl. XVII, fig. 5) has been added, presenting a *Spirillum* "*sporiferum.*" Of special interest, however, is figure 145, made after a picture published by *Kitt* (1899, p. 393), wherein numerous regenerative bodies are visible, budding out at the side or at the end of the rods, belonging to a *Bac. phlegmasiae uberis* (a member of the Aerogenes group).

That the colonies growing on the plate sometimes contain nothing but such round regenerative bodies, is illustrated by two photographs made by *Axelrad* (1903), reproduced as figures

146 and 147 on Plate XI. The former shows a contact preparate of *Streptococcus lanceolatus;* its large budding cells are especially noteworthy. The latter was taken from a colony of *B. coli.*

A rôle played by the gonidia in the multiplication of the bacteria, and the parallelism indicated thereby between tricho- and other bacteria, are also shedding some more light upon the physiological significance of the clubs formed by Mycobacteria and Actinomycetes, as well as by many other bacteria. As figure 43 on Plate L an old drawing, made by *F. Cohn* (1870), was reproduced, showing an interesting "club," attached in a lateral position to a Crenothrix thread, and considered by the author to be of a spore-like character. On Plate J as figure 34, a drawing by *Babes* (1895) was given, presenting clubs produced by a diphtheroid organism, one of them containing four small granules, while in the other one a larger spore-like body is visible. On Plate B as figure 3 another drawing made by the same author may be found; one of the Streptococcus chains sketched therein, has also attached to its side a club, which resembles very closely the Crenothrix club of *Cohn.* That the gonidia, or "spores," as *A. Neisser* called them, which are contained in the club-shaped cells of the diphtheriod bacilli may according to this author's observations (*A. Neisser,* 1888) germinate therein and grow out sideways was mentioned on page 97. In addition, on page 98, quotations from *MacFadyean* (1889), *Bostroem* (1890), and *Eppinger* (1890) have been given, which also indicated that relations seem to exist between the production of gonidia ("spores") within the threads of Actinomyces and the formation of the characteristic clubs. Concerning the latter *Crookshank* (1896, p. 437) made the following important statement:

> These club-shaped bodies represent organs of fructification, rather than the results of degeneration or death. The difficulty in accepting the view of their being entirely lifeless forms lies in the fact that the author has observed daughter cells growing from the mature clubs; and, further, in the bovine fungus the author has been able to trace the stages in the development of a single club to a completely formed rosette.

As figure 55 on Plate N a drawing, made by the same author (*Crookshank,* 1896, original fig. 12 on Pl. XI), has been reproduced, showing tubercle bacilli taken from the liver of a Rhea, with swellings at the ends of the rods, which were said to be "very suggestive of spores." Whether the apparent germination of some of the liberated "spores" visible in the picture has been a true sprouting was not ascertained. Some years earlier, however, *Coppen-Jones* (1893) had reported that he saw clubs of the tubercle bacilli grow out into numerous short hyphae, and later *Conradi* (1900) recorded the same occurrence with *B. mallei:* fine short lateral threads being produced by clubs, as well as by the older broad threads.

On the other hand, *Olsen* (1897) has emphasized that spore-forming bacilli, too, may assume the appearance of an Actinomyces. His drawing of *B. mycoides* grown in sand was reproduced as figure 20 on Plate F. It should be compared with *Babes'* sketch of a clubbed diphtheroid bacillus mentioned above, as well as with the picture of *B. tuberculosis* made by *Metchnikoff* (see fig. 38 on Pl. J) and with the description of *B. diphtheriae* given by *Hill* (quoted on p. 78). As in these two cases, the breaking off of clubs in the shape of oval bodies from the end of side branches of *B. mycoides* is clearly visible in figure 20, but in addition the formation of endospores within the clubs is also well illustrated. According to the Norwegian author the same phenomenon, viz., the production of one endospore within each club, was noticed with several cocci, sarcinae, and with other bacilli. A drawing made by *Dangeard* (1891) of his "*Eubacillus multisporus,*" reproduced as figure 56 on Plate N (from original fig. 4 on Pl. VIII), wins new interest in this connection. And it is worth mentioning, too, that on the one side *Olsen's* view is supported by analogous findings with spore-forming bacilli reported by *Cozzolino* (1900) and by *Johnson* (1912), on the other side by some observations made by *Babes* (1907 *a*) with *B. leprae,* and by *Schütze* (1908) in regard to *Actinomyces monosporus.* According to the first-named author the branched forms of *B. leprae* are inclined to produce terminal clubs, staining at the outside like the normal cells, while the bright center reacts like a spore; and *Schütze's Actinomyces monosporus* is characterized by always producing only one oval spore at each branch, which, though still easily stainable, was found to display a higher resistance than other Actinomyces spores. *Loele* (1908) at the same time secured further evidence, that at least some of the Actinomyces clubs clearly exhibit their character as

reproductive organs, viz., those containing numerous granules. They were classed by the author as "sporangia."

A very interesting drawing of what we now call regenerative bodies, made by *Henneberg* (1898) of an acetic acid bacterium (*Bact. oxydans*), is reproduced as figure 57 on Plate N (from original figure 1, whose magnification evidently was not properly determined). It furnishes a very clear insight into the mode in which these bodies are formed. The same reproductive organs were seen by *Henneberg* (1901) also with several lactobacilli, where they are, indeed, most frequent, but it is not easy to understand how the author, after having made those sketches of the acetic acid bacteria, now can state without hesitation:

An den Zellen kleben häufig mehr oder weniger grosse tropfenförmige Ausscheidungen aus den Nährflüssigkeiten, die den Zellen ein ganz verändertes Aussehen geben können.

B. Lindneri is declared to have shown "fettartige Ausscheidungen aus den Nährflüssigkeiten an den Zellen festgeklebt."

Tissier (1900) obtained the same round bodies with his *B. bifidus*, but he was careful enough not to discard them without trial; therefore, he was able to report:

De ces boules partent en rayonnant des corps bacillaires d'une grande finesse qui se subdivisent.

Sandberg (1904) made some good photographs of regenerative bodies attached to lactobacilli taken from the stomach, though not noticing them. *Weigmann, Gruber*, and *Huss* (1907) made pictures of the same "bulb-like inflations" growing at the end or at the side of lactobacilli from matzoon, and *Kuntze* (1908) photographed those of *B. bulgaricus.* None of these authors, however, saw them germinate. As figure 148 on Plate XI one of our photographs of *B. bulgaricus* (*Löhnis* and *Smith,* 1916 *a*, fig. 29) has been reproduced, showing two regenerative bodies in their characteristic position and also (below the upper one) two thin threads parting at the same place from a broader rod.

Analogus things have been repeatedly photographed. *Maassen* (1904), for instance, published a picture of a spore-forming bacillus isolated from chopped meat ("Hackfleisch"), which was reproduced as figure 149 on Plate XI (from original fig. 4 on Pl. XI), where it makes an interesting counterpart to our photograph of *B. bulgaricus,* as well as to *Olsen's* drawings of spore-forming clubs. In the textbook of *Hiss* and *Zinsser* (1914, p. 576, fig. 125) *B. subtilis* is photographed as reproduced in figure 150 on Plate XI, but in the text nothing is said concerning this remarkable outgrowth.

Small coccoid reproductive organs of *B. coli,* like those discussed by *Almquist* (1893), were closely studied by *Adami, Abbott,* and *Nicholson* (1899) and by *M. E. Abbott* (1900). To some extent they behaved like vegetative cells and were mentioned, therefore, already on page 56 But their ability to reproduce normal rods was also well noticeable. The authors connect them with the so-called polar granules, so common in *B. coli* and related species, and also with the "beading" often shown by the tubercle bacilli. Furthermore, *M. E. Abbott* points out that like *B. coli* other bacilli, too, may undergo such changes in the body, so that in fact many of the "granules" occurring within the tissue may be reproductive organs of different bacilli. A similar view has been expressed by *Wertheim* (1899) in regard to the gonococcus, as well as to staphylo- and streptococci. The small granules produced by these organisms are considered to be the reason why occasionally infections may be caused, though no cocci can be found. *N. K. Schultz* (1901) obtained analogous results concerning the plague bacillus. She observed directly in the hanging drop the upgrowth of the granules into normal rods, as shown on Plate O in figure 58, which was reproduced from her first paper (1901 *a*, original fig. I). Other interesting data have been furnished by *Rothert* (1902), unfortunately in a not easily accessible Russian dissertation entitled "Degeneration and Regeneration of the Bacteria." It was pointed out in this paper, probably for the first time, that all bacteria during their period of "degeneration" produce more or less resistant granules, which are enabled to act under suitable conditions as organs of "regeneration." The following species were studied, all with positive result: *Staphylococcus pyogenes aureus, Streptoc. pyogenes, B. coli, B. typhosus, B. pneumoniae, B. capsulatus Pfeiffer, B. rubidis, B. arborescens, Vibrio cholerae, V. Milleri;* and

it was especially criticized, with good reason, that too many bacteriologists are always ready to discard all cultures showing "granular decomposition" as dead, without having them first thoroughly tested. *Fedorowitch* (1902), another Russian bacteriologist, added important observations upon the germination of the "granules" produced by several cocci, *B. pyocyaneus, typhosus, coli, septicaemiae murium, cholerae gallinarum, diphtheriae,* and *tuberculosis,* which he studied in the hanging drop and for which he proposes the name "protospores," because they are, according to his opinion, reproductive organs similar to the regular endospores, though not reaching the full development and the high resistance of these latter forms. With his Enterococcus, *Thiercelin* (1903) found out that small granules, which the French author calls "microblastes," increase in size step by step until they reach again the normal size of the coccus. In addition, *Thiercelin* and *Jouhaud* (1903 *a*) discovered that the microblasts are produced by the liberation of the "granulations périphériques," which are growing within the cell alongside with the "taches centrales," which participate in the cell division. In some cases "un fin pédicule" was seen connecting parent cell and microblast. *Grassberger* (1903) saw and discussed formation and liberation of similar granules by *B. Chauvoei.* He describes the process as "Abschnürung unreifer Sporenanlagen" and makes in this connection the very appropriate remark:

> Gewöhnlich werden bei mikrophotographischen Darstellungen sporulierender Bakterien solche Stellen vermieden, in denen sich derartige losgetrennte Sporenanlagen vorfinden, da sie eine verdächtige, allerdings nur morphologische Ähnlichkeit mit Kokken aufweisen.

His photograph (original fig. 67) has been reproduced as figure 151 on Plate XI, where it furnishes a good counterpart to figure 152, a copy of a photograph made by *Winogradsky* (1902, original fig. 1) from his Clostridium Pastorianum. The coccoid forms are easily discernible, in reference to which the author says:

> An den Fäden beobachtet man manchmal einen seltsamen Vorgang, nämlich die Abschnürung von kleinen, kokkenartigen Gliedern in mässiger Menge, welche, soviel ich weiss, nicht mehr entwicklungsfähig sind.

Experiments with several nonspore-forming bacteria (*Pseudomonas cerevisiae, fluorescens* and related forms) led *Fuhrmann* (1906–1913) to the conclusion that some of the metachromatic granules appearing within the cells, especially within the club-shaped ones, are reproductive organs to be compared with the endospores produced by the spore-forming bacilli. That he was not correct in regard to the second statement is beyond question. All bacteria, spore-forming and nonspore-forming alike, use their gonidia as one mode of multiplication and reproduction, while the more or less highly resistant endospores have their special task as resting forms, in which respect they can be replaced by the gonidia only to a very limited extent. But *Fuhrmann* was undoubtedly right in regard to the reproductive character of the "granules" studied by him, and it is only to be regretted that also his careful studies have not been considered and tested adequately. The development of new rods from the granules in the clubs and their liberation, as studied by him in the hanging drop, prove once more that this process is by no means so "impossible," as it was declared to be by *Migula* (1904).

That coccoid reproductive organs may play an important part in the life history of the tubercle bacillus was already indicated by those early observations of *Klebs, Babes, Malassez* and *Vignal, Biedert* and *Sigel,* and others, mentioned on page 95, by which it was also ascertained that some of these granules are acid-fast like the bacilli, while others are not, but that these can be stained by a modified Gram method, worked out by *Biedert* and *Sigel. Schürmayer* (1898 *a*), too, noticed that smaller and larger not acid-fast granules may be formed by the tubercle bacillus, which in their turn reproduce typical rods and are, according to this author, "undoubtedly spores." To globular bodies of the tubercle bacilli seen by *Arrigo,* which were reproduced from his drawings as figures 103 and 104 on Plate IX, are probably also to be classed, at least in part, as reproductive organs. The Italian author called them "germ granules" (Keimkörnchen). *Chester* (1901, page 14) was of the opinion "that these granular particles" (replacing the tubercle bacilli in old lesions) "are resting bodies of the nature of gonidia, which are capable of reproducing the species." What *Spengler* (1905–1907) described as fragments ("Splitter") of the tubercle bacilli is evidently of the same class; later they were declared by

him and by *Betegh* (1908) to be "spores." *Much* (1907–1909) paid special attention to the not acid-fast but Gram-positive granules. He emphasized strongly that they never had been seen before and that they were "entirely" different from the acid-fast globular bodies studied by *Spengler* and others. That both statements are not valid can be easily seen from the earlier publications, as well as from those contributed more recently by *Fuchs-Wolfring* (1908), *Knoll* (1910), *Fontes* (1910), *Kirchenstein* (1912), *Heinrich* (1912), and others. The acid resistance of these globular bodies naturally changes like that of the rods. Their slipping out of the sheath and their ability to reproduce small rods, which afterwards grow up to normal size, has been repeatedly observed by these authors. *Fontes'* paper is of special interest, because the filterability of a part of these "granules" was also studied in this case, and *Heinrich* has shown that "Much's granules" are equally present in Corynebacteria, *B. erysipelatos suum* and other not acid-fast, but Gram-positive species. *Rosenblat* (1905), too, observed in the hanging drop, that granules were formed within tubercle, leprosy and other bacilli, which were liberated after 7–9 days and then grew up to new rods and threads. But later (1911) she made the following somewhat surprising statement:

Es liegen keine Beweise dafür vor, dass die Muchschen Granula Entwicklungsformen oder Dauerformen der Tuberkelbacillen sind.

Leschke (1911) tried to correct this mistake.

With the diphtheria bacillus and its relatives the situation is very similar; but the contributions upon this subject are less numerous. "Cocci" have always played an important role in the diagnosis of diphtheria, as well as in the cultures obtained in such cases, from the time of *Oertel* (1871) until recently (*Walker* and *Adkinson*, *Mellon*, *Heinemann*, 1917), as was discussed on pages 77–81. *A. Neisser's* work on the "spores" of *B. xerosis* was mentioned in this chapter (p. 97). In addition, it may be quoted that *Babes* in a few cases found heat-resistant spores with genuine diphtheria bacilli (*Cornil* and *Babes*, 1890, Vol. II, p. 59), and *Chester* (1901, p. 14) thought it very likely "that the granular segments which they often produce are of the nature of gonidia." Additional interesting data are to be found in a paper upon the "Klebs-Löffler bacillus," written by *Bergstrand* (1918).

Coccoid reproductive bodies in leprosy have been also seen quite frequently. Besides those early discoveries of *A. Neisser*, *G. A. Hansen*, *Babes* and *Lutz*, the more recent findings of *Betegh* (1908) and *Kedrowski* (1910) are to be mentioned. Both authors studied especially those only partially acid-resistant forms, which were reproduced in figures 153 on Plate XI and 154 on Plate XII (from *Kedrowski's* original fig. 38 on Pl. VII). The latter are presenting an interesting counterpart to the round bodies found by *E. de Negri* (1916) in serum cultures of Corynebacteria, reproduced as figure 101 on Plate IX, and to similar round cells discovered by *Ghon*, *Mucha* and *Müller* (1906) in meningitis, here acting as reproductive organs of the anaerobic bacilli, shown in figure 10 on Pl. C. Figure 155 on Plate XII is a reproduction of the growth found in cuts from the brain (original fig. 3); figure 156 presents the typical appearance of the regenerative bodies grown anaerobically on glucose agar (original fig. 18); and figure 157 is a copy of a drawing made by *Neelsen* as early as in 1880 (original fig. 9 on Pl. XI) of the regenerative bodies of *B. cyanogenes*. This author already found out that the round bodies, which he compares with small yeast cells, are the result of the upgrowth of the gonidia formed by the rods, that they are either motile or immotile, that they stain very darkly, and that they are able to reproduce the normal rods when transferred at the right time.

The round bodies visible in figure 158 on Plate XII, photographed by *Hammerl* (1906, original fig. 4), belong to *V. cholerae*. *Bittrolff* (1912) and *Stamm* (1914) studied the same motile, budding globules, which were seen to germinate under suitable conditions to typical cholera bacilli.

Most extensive studies upon these "granular" and "globular" reproductive organs, which we call the gonidia and regenerative bodies of the bacteria, have been made within the last decade in regard to the spirochaets. It is evident that so much valuable material was secured in this case, because the investigators, most of them coming from the protozoological side, have not been blinded by the adverse bacteriological doctrine, and, therefore, they succeeded

despite the fact that these modes of reproduction are much more difficult to study with spirochaets than with any of the common bacteria. *Dutton* and *Todd* (1905), *Castellani* (1905), *Wechselmann* and *Löwenthal* (1905), *Leuriaux* and *Geets* (1906), *Krienitz* (1906), *Breinl* and *Kinghorn* (1906), as well as *Perrin* (1906), have furnished the earliest contributions, establishing the fact that "metachromatic" or "chromatine" granules produced within the spirochaets may either multiply as such and replace the spirochaets temporarily in the organism, or eventually reproduce the long forms, and that not infrequently larger "bulbs" are visible at the side or at the end of the spiral organisms, which also seem to act as reproductive organs. That cysts formed by coiled spirochaets may equally participate in this process was made probable by the investigations of *Breinl* (1907) and of *Dutton* and *Todd* (1907). Among the numerous further studies which tried to elucidate these difficult problems those of *Leishman* (1909–1918), *Balfour* (1911–1913), *Fantham* (1911), *Hindle* (1911), *Noguchi* (1911–1912), and *Henry* (1913) may be mentioned here. An illustration by *Fantham* (original fig. 5) has been reproduced as figure 59 on Plate O. The formation and liberation of the "spores" as shown here, invites a comparison with *Perty's* old drawing of granulated spirilla visible in figure 42 on Plate L, and with the liberation of the gonidia by some bacteria as it was drawn by *Billroth* and reproduced in figures 44 and 45 on Plate L. Two drawings made by *Bosanquet* (1911 original figs. 21 and 22) of *Spirochaeta anodontae* may be added as figure 60 on Plate O. It is interesting to see how very closely the results of these new studies upon the life history of the spirochaets agree with those recorded nearly 40 years ago by *Heydenreich, Guttmann* and *Albrecht,* which were mentioned on p. 94.

As figure 159 on Plate XII a photograph of an anaerobic bacillus, probably belonging in the Fusiformis group, has been reproduced, which was made by *Rosenow* and *Tunnicliff* (1912, original fig. 3 on Pl. I). Liberated "granules" are well visible, as is also their escaping and budding out from rods and threads.

That the gonidia of pathogenic bacteria may play an important rôle as filterable vira and cell inclusions has been emphasized by *Herzog* (1910–1913) with regard to the Gonococcus. The observations upon the "infective granules" of the spirochaets in tick fever, and spirochaetosis of fowls, recorded by *Leishman, Balfour* and others of the authors just mentioned, the relation between spirochaets and filterable virus in hog cholera, as discussed by *Rüther* (1910) and *King* et al. (1913), and the recent discoveries of *Rosenow* et al. (1916–1917) upon the small forms of a Streptococcus as causative agent in poliomyelitis, as well as those of *Hort* and his collaborators, to be discussed presently, indicate beyond doubt that these problems will become the more important the more thoroughly the gonidia of the bacteria will be studied.

In some experiments carried out with *B. bifidus Noguchi* (1910) was able to demonstrate for the first time that it is possible to induce regular spore formation with otherwise not spore forming bacilli, and also to cause their reversion to the original type.

The first special information upon gonidia and regenerative bodies ("Regenerationsformen"), produced by Azotobacter, was furnished by *Prażmowski* (1912, p. 145, 167), and of still greater value are additional investigations of the same author (*Prażmowski,* 1913), wherein he reached the conclusion that probably all bacteria are able to liberate small granules of nuclear material which act as reproductive organs. The first photographs of the flagellated gonidia of Azotobacter made by *D. H. Jones,* have been reproduced as figure 160 on Plate XII (from original figs. 9 and 10 in Pl. V); although not clearly defined they illustrate the liberation of the gonidia from the disintegrating larger cells, and with some difficulty their long cilia may be discerned. Another photograph, reproduced as figure 161 on Plate XII, was made by *Marrassini* (1913, original fig. 28 on Pl. I); it shows several gonidia of *B. subtilis,* a few of them with long single cilia, though the author himself had only in mind to show the capsule and flagella around the Subtilis rods, apparently not noticing the many round bodies, despite their predominance.

A casual observation concerning endospore formation in some or our old Azotobacter cultures led to the discovery of the striking pleomorphism of this group of organisms (*Löhnis* and *Hanzawa,* 1914). Copies of three of the photographs published in this paper were given as

figures 19–21 on Plate II; the breaking up of the larger cells into the smaller "granules," first discussed by *Prażmowski,* is clearly visible in the first two of them. The perfectly round forms of medium size, which were also shown in one of the photographs of that paper, reproduced as figure 68 on Plate VI, are to be classed as regenerative bodies. A comparison of this picture with figure 35 on Plate III (*B. pestis, Rowland,* 1914), figure 59 on Plate V (*B. anthracis, Henri,* 1914), figure 91 on Plate VIII (*B. mallei, Carpano,* 1913), figures 101 and 104 on Plate IX (*Corynebacterium, E. de Negri,* 1916, and *B. tuberculosis, Arrigo,* 1900), figures 154, 156, and 158 on Plate XII (*B. leprae, Kedrowski,* 1910, the anaerobic meningitis bacillus of *Ghon, Mucha* and *Müller,* 1906, and *V. cholerae, Hammerl,* 1906) will make it clear that the surprising uniformity of this globular type of regenerative bodies as produced by all groups of bacteria is certainly a point of considerable importance.

In his "Studien über die Fortpflanzung von Bakterien, Spirillen and Spirochaeten" *Meirowsky* (1914 *b*) has furnished very valuable information upon the production and development of gonidia and regenerative bodies by representatives of different groups of bacteria, once more demonstrating the general occurence of these modes of reproduction. Many details secured by him, will have to be discussed on the following pages. As figures 162–167 on Plate XII some of his drawings are reproduced, illustrating what he calls the formation of "buds" and "umbels" ("Knospen" and "Dolden") by B. *tuberculosis* (figs. 162–164), *B. leprae* (figs. 165–166), and by *Spirillum rubrum* (fig. 167). But *Meirowsky,* too, furnishes an excellent example of what disadvantageous effect may result from an uncritical submission to the prevalent theory, when he concludes from his observations, that tubercle and leprosy bacilli should be separated from the bacteria on account of their forming "buds" and "umbels," and should be placed among the fungi, because, according to his opinion, such modes of multiplication and reproduction are entirely absent in bacteria; and yet he himself found exactly the same facts with *B. paratyphi B, B. enteritidis,* spirilla and spirochaets, and concludes, on the other hand, that the spirochaets, therefore, ought to be classed among the bacteria. The following quotations will prove this curious lack of logic.

Das Auftreten von Seitenknospen, Dolden and Seitenzweigen stellt die Tuberkelbacillen ausserhalb der Reihe der Bakterien und lässt sie zu höheren Pilzformen in Beziehung treten, in deren Entwicklungskreis sie vermutlich gehören (p. 11).

Betrachtet man den Leprabacillus vom rein morphologischen Standpunkt, so ergiebt sich, dass er nicht zu den Bakterien gerechnet werden kann, da bei diesen nur die Vermehrung auf dem Wege der Querteilung und Sporenbildung stattfindet (p. 15).

Concerning *B. paratyphi B:*

Auch hier zeigt sich wieder, dass ein kugliges Gebilde ausserhalb des Bacillenleibes liegen und mit ihm durch einen feinen Stiel verbunden sein kann; (und es) sind teils gegliederte, teils ungegliederte Fäden vorhanden, die an ihren Enden eine Dolde tragen (p. 15, i. e., on the same page bearing the statement in regard to the leprosy organism).

Concerning *B. enteritidis:*

Neben ihm lag häufig ein kugliges oder auch mehr längliches Gebilde, das in zahlreichen Fällen mit ihm durch einen Stiel verbunden war . . . Die weiteren Bilder zeigen, . . . dass diese Knospen . . . zu langen . . . Fäden auswachsen können. Diese Gebilde weisen häufig . . . kuglige Auftreibungen, Seitenknötchen und vor allem Seitensprossen und Verzweigungen auf (p. 16).

Concerning spirochaets:

Es muss . . . betont werden, dass dieser Knospenbildung eine ausserordentliche Bedeutung fürdie Vermehrung der Spirochaeten zukommt (p. 59).

That, in fact, the processes studied by *Meirowsky* are quite general with and typical for all bacteria, and that, therefore, they can not be used as a reason for separating tubercle and leprosy organisms from other bacteria, has been presented, moreover, by *Meirowsky* in the same paper very clearly in a graphic summary (Pl. XVIII), which has been reproduced as Plate XIV.

Evidently without knowledge of this German publication *Hort* in England published a series of reports (*Hort* et al., 1915–1917), which on the one side furnish much confirmative material with regard to *Meirowsky's* and *Almquist's* discoveries, and on the other side open a wide new field for further research upon pleomorphism and reproduction of the bacteria, especially in

connection with the so-called filterable vira. On Plate XIII as figure 178 a collection of drawings made by *Meirowsky* (original plate III), illustrating the various phases in the life history of *B. paratyphi B*, has been placed side by side with two pictures made by *Hort* (1917*a*, original figs. 1 and 2) of *B. typhosus* (fig. 179), and of *B. coli* (fig. 180), which deserve to be studied closely. The remark made by *Adami* (1916) after having become acquainted with *Hort's* investigations, which was quoted on p. 10, will present itself as being, indeed, very appropriate, when considering the many data discovered or rediscovered recently with regard to bacterial reproduction, which have always been discarded by the "simplicity" doctrine, still widely prevailing among bacteriologists and in bacteriological literature. With the meningococci *Hort* (1917*b*) once more discovered that type of multiple production of gonidia within the enlarged parent cell, which was declared by *Migula* to be "impossible," though, in fact, it has been studied by many investigators and is so common with all groups of bacteria that *Hort* undoubtedly was mistaken when he thought the Meningococcus must be placed among the Hemiascomycetes on account of its "gemmation and multiple endosporulation."

A short summary of our own investigations upon the different modes of bacterial reproduction (*Löhnis* and *Smith*, 1916*a*) was quoted on p. 90, and several details will have to be mentioned on the following pages. Some of our photographs, which were demonstrated at the New Haven meeting of the "Society of American Bacteriologists" (1916*b*), are reproduced as figures 168–176 on Plate XII, illustrating formation and liberation of gonidia of *Micr. candicans* (fig. 168) and *M. luteus* (fig. 169), development of the regenerative bodies by *Streptoc. lactis* (fig. 170), *B. pneumoniae* (fig. 171), and *B. bulgaricus* (fig. 172), germination of regenerative bodies of *Azotobacter Beijerinckii* (fig. 173), development of new small organisms from the gonidia while still connected with the parent cell (fig. 174, *B. fluorescens*; fig. 175, *Azotob. vinelandii*) and a star-like upgrowth of small rods from an agglomeration of unstainable gonidia liberated from the large darkly stained cells of *Azotob. chroococcum*, visible in the lower part of the picture (fig. 176). The many relations to and confirmations of earlier observations quoted on the preceding pages are evident. And it is equally obvious that the various forms visible in figure 177, which is a reproduction of a photograph made by *Goadby* (1917, original fig. 14) of a bacillus isolated from gas gangrene, which could not be identified "owing to the curious method of growth," are an interesting collection of gonidia, regenerative bodies and endospores.

It goes without saying that, like the pleomorphism of the bacteria in their vegetative stage, so also their different modes and organs of reproduction will necessitate much more thorough investigations than those generally en vogue now as at *Robert Koch's* time. It is easy, but not scientific, to get quickly rid of all unexpected facts by declaring them to be involution forms, contaminations, artefacts, plasmolysis, plasmoptysis, etc., without making any special test. Such special tests, however, are of course indispensable if correct results are to be obtained.

(b) DIFFERENTIATION BETWEEN REPRODUCTIVE ORGANS AND OTHER CELL PRODUCTS AND ARTEFACTS.

Undoubtedly, the reproduction of a new bacterium is the only fact by which it is possible to decide with absolute certainty whether or not a problematic body is a reproductive organ of a bacterium. The observation of active motility often shown by the gonidia, and sometimes by regenerative bodies, too, furnishes also fairly conclusive proof. In many cases, however, the examination of the stained preparate must be used as basis for judgment, and here the road is beset with numerous pitfalls. Thus far many investigations have been made upon the bacterial cell and its content, without paying any attention whatever to the possibility, that some of the cell products might have been reproductive organs other than endospores in different stages of their development. It is not only probable, but even certain to some extent, that among the cell inclusions described as nuclear material, chromatin, metachromatic granules, volutin, glycogen, fat and other reserve material, as well as vacuoles, growing gonidia and regenerative bodies have been included, because their staining reactions, changing in the course of their development, have established an apparent relationship to the one or to the other class of cell products. Detailed studies, as have been made in this respect with

growing endospores, are nearly entirely missing at the present time with regard to the other bacterial reproductive organs. Nevertheless, the cytological results collected so far also contain several valuable indications, which may be helpful for further research; therefore, they will have to be considered first.

The time is not far back when there was much discussion concerning the presence or absence of a nucleus in the bacterial cell. The results available now, though by no means final, can be accepted, however, as sufficient evidence that arrangement or distribution of the nuclear material changes during the life of the bacterial cell and varies to some extent with the different species. Uniform distribution, similar to the "chromidia" in the protozoa, arrangement in circles, spirals, zigzags, rods, chains, or filaments, as well as concentration into one or two distinct bodies, displaying the qualities of true nuclei, have all been observed within the same cell and with representatives of very different groups of bacteria. Publications by *Zukal* (1896), *Vejdovsky* (1900–1904), *Mencl* (1905–1911), *Perrin* (1906), *Swellengrebel* (1906–1909), *Guilliermond* (1908), *Růžička* (1908–1909), *Hölling* (1910), *Dobell* (1911), *A. Meyer* (1912), *Prażmowski* (1912), and *Luska* (1914) have accumulated much valuable material in this respect, against the older widely divergent views held by *Bütschli* (1890–1896), *A. Fischer* (1897–1903), and *Migula* (1897). It can not be further doubted that nuclear material plays the same important rôle in regard to growth, division, and multiplication of the bacterial cells as it does in the cells of the higher organisms. That it will always participate in the formation of reproductive organs is equally beyond doubt, despite the scantiness of experimental proof available at present.

Some interesting observations concerning the production of zoospores have been made by *Zukal* (1896) in connection with his cytological studies. He noticed that the nuclear granules, which he calls "microsomes" and which he found to be frequent in bacteria, protozoa, and Cyanophyceae, are able, especially in the latter case, to assume under certain circumstances the character of regular zoospores. That the chromidia of protozoa may reproduce new cells has been recorded very often. Motility, fission, and participation of "chromatin granules" in the division of the bacterial cell have been studied by *Babes* as early as in 1885. Their predominant part in the formation of bacterial endospores has become known especially by the investigations of *Zettnow* (1899), *Schaudinn* (1902–1903), *Guilliermond* (1908), *Růžička* (1908–1909), *A. Meyer* (1912), and *Swellengrebel* (1913). That the spores of Actinomyces are also of nuclear character was pointed out by *Neukirch* (1902), and the granules (i. e. gonidia) of the tubercle bacilli were declared by *Fontes* (1910) to be made up prominently of paranucleo-albumin. The so-called sporoids, replacing sometimes the regular endospores in spore-forming bacilli, are also chemically equivalent to them, as far as can be derived from microchemical analysis, according to *Růžička* (1908–1909) and *Petschenko* (1913). The formation of the so-called spores (i. e. gonidia) of *Spirillum volutans* went on, as was pointed out by *Amato* (1908), practically in the same manner as the formation of the endospores in *B. mesentericus*, *subtilis*, and *mycoides*. That some of the nuclear material may leave the old cells has been noticed by *Rowland* (1899) and by *Mencl* (1911), but it is to be doubted whether this is merely an excretory process, as these authors are inclined to believe, or whether these liberated granules have not been actually gonidia. Probably the work done by *Prażmowski* (1912–1913) will prove most valuable as a basis for further investigations in this direction, as here the reproduction of new cells from the nuclear granules has been studied inside as well as outside of the parent cell. In addition some very suggestive work done with yeasts also deserves our attention. *Eisenschitz* (1895) collected valuable data concerning the staining qualities, motility, division, and arrangement of nuclear granules in yeast cells and about their participation in budding; and *Hest* (1907) contributed a highly interesting article on "pseudo-vacuoles" and "pseudo-nuclei" in yeasts, showing that the frequently mistaken "granules" in this case too acted clearly as reproductive organs, very much like the bacterial gonidia. Some of his drawings and photographs could be readily accepted as illustrating analogous processes in the life of Azotobacter.

The chromatin granules have usually attracted most of the attention of the various investigators, whose results, however, diverge widely, a fact not difficult to understand. With regard to the higher organisms the chromatin has been declared to be "the vehicle in which the constitutional structure, primarily of the species and secondarily of recent ancestors and parents is represented" (*Spencer*, 1898, p. 264). With the bacteria at least in the case of endospore formation the concentration of the chromatic substance has been always noticed, though especially in ripe old spores the presence of other substances may occasionally greatly affect the microchemical reactions, which fact, studied especially by *Zettnow* (1899), has misled some authors like *Růžička* (1913) to believe that the chromatin "vanishes" in old spores. Again, with regenerative bodies and gonidia the analogous change in stainability may occur, though it is generally less frequent than with endospores. Growing gonidia and regenerative bodies, however, will always, like growing endospores, exhibit the chromatin reactions very clearly. Thus far the chromatin granules present in the bacterial cell have been accepted by the various authors as being of very different physiological value, an opinion which is undoubtedly justified to some extent, but which at the present time is usually much more based on assumption than on evidence. This is particularly true in regard to such cases where the ever-ready hypothesis of "involution forms" has been invoked indiscriminately. *Beck* (1903, p. 777), for instance, does not hesitate to declare:

So viel steht fest, dass die Differenzierung des Plasma des Bakteriums und damit auch die Bildung der chromatischen Substanz in demselben mit der Vermehrung und Fortpflanzung des Bacillus nichts zu tun hat.

But in the same "Handbuch," which contains this highly surprising statement, *Gotschlich* (1903, p. 83) connects the granules with an increased resistance of the cells and *Wladimiroff* (1903, p. 722) is certain about their reproductive character. *A. Fischer* (1897, p. 122; 1903, p. 8) classes them as reserve material; to *Migula* (1897, vol. I, p. 89) they are the beginning of nucleus formation. *Swellengrebel* (1907) saw round bodies of a "very complicated inner structure" develop in the center or at the end of the cell, but they, too, are to him "merely involution forms." *Petschenko* (1913) distinguishes those chromatin parts which are becoming "sporoids" (gonidia), from others participating in the metabolism of the cell, by the fact that the latter according to circumstances may increase and decrease in size, while the former show only an upgrowth, a fact evidently not easily to be ascertained and probably not always valid. Whether an observation made by *Bütschli* (1896, pp. 40–43) will be a helpful hint for recognizing growing gonidia, remains to be seen. This author noticed that the centrally located chromatin granules turned blue when stained with methylen blue, while those at the periphery, though reacting with Delafield's hematoxylin like those in the center, exhibited metachromatic qualities, becoming red with methylene blue. It is not impossible that there may be some relations between these findings and those recorded by *Thiercelin* (1903) concerning the "taches centrales" and "granulations périphériques," mentioned on p. 104, though it would be undoubtedly a serious mistake to assume that gonidia and regenerative bodies will always originate close to the cell wall; there is sufficient evidence on hand that at least the growing gonidia are often to be found in a central position and their diameter is not infrequently as large or even a little larger than the width of the parent cell.

The polar granules have been frequently looked upon as being enabled to assume a reproductive character, though the results obtained have been much at variance. So it has been the case with *B. typhi, coli, V. cholerae,* and *V. Finkler-Prior,* as may be seen, for instance, from the papers by *Ermengem* (1885), *Finkler* and *Prior* (1885), *Buchner* (1888), *Adami, Abbott* and *Nicholson* (1899), and by *Escherich* and *Pfaundler* (1903). That in the textbooks the polar granules are usually classed as "merely degenerative" or "simply artefacts" is in accordance with the generally prevailing practice; and it is, of course, indisputable that rough handling of dried smears may cause the appearance of plasma clumps looking like polar granules, but not having their physiological value, and, therefore, furnishing no proof whatever in regard to the meaning of those polar granules, which are present in the living cell. *N. K. Schultz* (1901 *a*) made some interesting observations concerning the reproductive function of the polar granules in old cells of the plague bacillus, as may be seen from her drawings reproduced as

figure 61 on Plate O (from original fig. II), illustrating the development of the polar granules to a uniformly distributed cell content. *Baur* (1905) has shown that polar granules participate in the formation of the arthrospores produced by Myxococcus; and that they are equally connected with the development of endospores has been frequently observed. Their independent acting as reproductive organs, however, remains to be studied more thoroughly, before any well-founded answer can be given.

The metachromatic granules, which *Babes* (1889) first found to be frequent with all kinds of bacteria, especially in older cultures, have been characterized in that paper, besides by their being stained violet by methylene blue, by their ability to reproduce new vegetative cells and by their acting in this direction as counterparts to endospores, though not exhibiting such an exceptional resistance against heat and drying. In a second paper (*Babes,* 1895) they were declared to participate in cell division, as well as in the formation of spores, buds, and branches; and in a third contribution (*Babes,* 1914) the so-called Much's granules of the tubercle bacillus were identified with them, and their rôle as reproductive organs was once more emphasized. To *A. Fischer* (1897) their metachromatic behavior was merely caused by the assumed fact that the accumulation of the stain within was said to prevent the passage of light, so that only the reddish reflex characterstic of methylene blue remained noticeable. *Guilliermond* (1910), who next to *Babes* studied the subject most intimately, contests this author's interpretation, as well as that preferred by *A. Meyer* (1903), who identifies the metachromatic granules with his so-called volutin. According to the French author, metachromatic granules are produced not only by all bacteria, but also by all protozoa, yeasts, other fungi, as well as by higher organisms; which statement leaves hardly any doubt, that, in fact, rather different objects have been grouped together. If, therefore, other authors like *Jordan* (1909, p. 58), *Frost* and *McCampbell* (1910), and *Dobell* (1911) assume that the metachromatic granules are some kind of reserve material, but do not participate in the life of the cell, though *Fedorowitsch* (1902) and *Fuhrmann* (1906) have demonstrated that growing gonidia, regenerative bodies, as well as spores, also exhibit, at least temporarily, metachromatic reactions, such conflicting statements are, indeed, not so irreconcilable as they may seem to be at the first moment. The large metachromatic globules, which *Hölling* saw in old spirilla cultures and which he interpreted as volutin, despite their ability to divide themselves, will also have to await a more correct classification. The same holds true concerning those metachromatic granules which were found in and outside of "Mastzellen" and were classed as metabolic products by *Bargum* (1903) as well as by *Guilliermond* and *Mawas* (1908). That some of them may be gonidia or regenerative bodies of bacteria is just as well possible as was the case, e. g., with the round bodies seen by *Hibler* in and outside of "Mastzellen" accompanying the bacilli of symptomatic anthrax, and also in the pure cultures of this organism, as was discussed on p. 67. *Ross* (1912) pointed out specifically that the large spherical bodies studded with chromatin granules, which are produced by spirochaets (as well as by other bacteria in their symplastic stage) can be easily mistaken for mast cells.

The granules first described by *P. Ernst* (1888), and usually called accordingly, have been often identified with *Babes'* metachromatic granules, for instance by *Bütschli* (1890), *A. Fischer* (1897), *Marx* and *Woithe* (1900), *Kamimura* (1903), *Bonazzi* (1915), and others, though their solubility in boiling water differentiates them from *Babes'* granules, whose relation to reproductive organs is certain, at least to some extent, as with the granular form of tuberculosis, mentioned above. When *Coppen-Jones* (1895) maintained that *Ernst's* granules be growing "spores" of the tubercle bacillus, he also evidently meant *Babes'* granules, and the great difference which exists between the claims made by *Marx* and *Woithe* (1900) concerning the rôle played by the "Babes-Ernst" granules in the life of pathogenic bacteria, and the results recorded by their opponents like *Ficker* (1903), is due undoubtedly to the study of different things, all included under the same conventional term. It is true that *P. Ernst* himself in his first paper (1888) dealt prominently with *B. xerosis* and its sporeformation, as studied by *A. Neisser*, and in his second paper (1889) he calls the inclusions directly "sporogenous granules," though evidently many of them, as described and illustrated in the paper, have nothing to do with the formation of spores or other reproductive organs; in a more recent paper (*P. Ernst,* 1902), too,

some of the bodies show again marks of having been gonidia (budding, fission, and motility after liberation). Nevertheless, it has become such a general practice to ascribe to "*Ernst's* granules" solubility in boiling water, since *Bunge* (*1895*) and *Mühlschlegel* (1898) have differentiated their "sporogenous" granules from them in this way, that it will be preferable to adhere to this practice, and to use this method for differentiating between soluble and insoluble metachromatic granules, and for obtaining eventually more information upon their relations to the various reproductive organs.

That the staining reaction not infrequently changes during the development of the gonidia and regenerative bodies, though usually not to such an extent as with the endospores, has been frequently noticed in the course of our studies. While usually well accessible to aqueous dyes especially to fuchsin, gonidia as well as regenerative bodies sometimes become hard to stain, a point which has been studied to some extent by *Kuntze* (1904) with regard to the gonidia ("Schwärmer") of *B. oxalaticus*. In most cases, however, the comparatively very dark color of the stained regenerative bodies is very conspicuous, as may be also seen from the photographs reproduced on several of our plates. In addition, aqueous fuchsin often causes a peculiar tint of red with regenerative bodies, which is well discernible after sufficient training of the eyes.

As no sharp microchemical differentiation is possible at present, and possibly never will be, between chromatin and metachromatic granules on the one side and growing reproductive organs on the other, so also fat, glycogen, and other so-called reserve material will be used in smaller or larger quantities by the bacterial cell for building up its reproductive organs, and, therefore, the more or less characteristic reactions of these substances will be also noticeable with growing gonidia, regenerative bodies, and spores. It would be, of course, a serious mistake to draw rashly final conclusions from such tests, and it should also be constantly borne in mind when making microchemical experiments with bacteria, that these reactions are by no means so prompt and reliable as one might be inclined to believe after having read, for instance, the books of *A. Meyer* (1903–1912). On the other hand, it would be equally unwise to share such an extreme standpoint as was taken by *A. Fischer* (1899), who felt compelled to fight against the "staining mania" ("Färbungstaumel"), mostly because he got all kinds of reactions and artefacts under conditions which were rather different from those prevailing in bacteriological tests. The following statement made by *Kruse* (1910, p. 48), however, may be accepted as fairly correct:

> Man traut . . . den meisten mikrochemischen Identifizierungsverfahren doch zuviel zu.

Fat has always taken the most prominent place among the substances used for "explaining" the presence of various granules within the bacterial cell. *R. Koch* (1876) was quite positive that the Anthrax spore be made up of a bright droplet of some kind of oil, covered by a thin protoplasmatic layer. And at present often a staining with sudan, etc., is considered to be sufficient evidence to establish the presence of "fat droplets" inside or outside of the cell, though it may have been gonidia containing some fat, but, of course, also all other substances necessary to a continuation of bacterial life. *Büsgen* (1894) felt completely justified to reject the findings of *Zopf* (1881) and *Billet* (1890) concerning the globular gonidia produced by *Cladothrix dichotoma*, because he was able to "solve" these "fat granules" by treating them with hot alcohol. In fact, however, he merely extracted some fat from what he calls a "vacuoliges Protoplasmagerüst," and the direct observations, made by the earlier authors upon the germination of these bodies, are, of course, also not eliminated by this extraction. The manner in which *Henneberg* (1901) classed as "fat droplets" what has been evidently the very conspicuous regenerative bodies of lactobacilli, was criticized on page 103. In publications of *P. Eisenberg* (1909) and *Vahle* (1909) the "fat" hypothesis plays an equally prominent rôle. *Kruse* (1910, p. 48), too, accepts the fat reactions as full proof that, e. g., the so-called sporogenous granules not only contain some fat, but that they are nothing else than "fat droplets." On the other hand, *Altmann* (1894, pp. 101–104) has already pointed out that the cell granules which participate actively in the cell life of the higher organisms may also assimilate considerable amounts of fat without reducing their vital activity even if

they appear micorochemically like large fat drops. With Blastomycetes, *Casagrandi* (1897) found out that such apparent fat granules react like nuclein and protein substances after the fat has been extracted by alcohol. The "swarming bodies" of *B. oxalaticus* have been tested by *Kuntze* (1904) also with the result, that they may contain, but that they are not, fat; and the same has been said concerning similar "sporoids" by *Růžička* (1909), *Vay* (1909), and *Ambrož* (1909), especially against *P. Eisenberg*. The protein reaction has been quite evident as far as tests have been made in this direction. That especially the granules of the tubercle bacilli contain albuminous together with fatty substances was ascertained by *Deyke* (1910) and confirmed by *Babes* (1914), who compares them also in this respect with the endospores of the bacilli.

Besides fat, according to *A. Meyer* and his pupils, volutin is to be credited with playing an important rôle as reserve material in the bacterial cell. The fact, however, that it is declared (*A. Meyer*, 1912, p. 204) to be absent in spore-forming bacilli, Pseudomonas, Streptococcus and Sarcina, does not support this view, and as this "volutin" admittedly belongs to the protein substances, more thorough tests of the so-called volutin globules especially in spirilla seem to be necessary; they bear a suspicious resemblance to those other globules which were found by some authors to be without any significance, while others have seen them germinate quite readily and grow up to new spirilla. *Dietrich* and *Liebermeister* (1902), as well as *Růžička* (1908), have already critized the volutin hypothesis. *Prażmowski* (1912, p. 157), too, calls this substance "highly problematical;" and *Minchin* (1915) is convinced,that the "infective granules" (i. e. gonidia) of trypanosomes (spirochaets) have been frequently mistaken as "volutin."

The "granules" and "globules," visible in and outside of the bacteria, have also been often readily accepted as glycogen, merely on account of the brown color sometimes exhibited by them when treated with iodine. That this reaction is by no means very stable has been frequently noticed. The round buds ("Aussprossungen") of *B. radicicola*, e. g., showed, according to *Hiltner* and *Störmer* (1903), often but not always glycogen reaction. The inflated forms of *B. Chauvoei* were found by *Hibler* (1908) to turn brown, violet, or yellow. Similar inconsistencies have been discussed by *Prażmowski* (1912, p. 158) with regard to Azotobacter. *Kuntze* (1904) noticed that the swarming bodies of *B. oxalaticus* turned yellow at the outside, brown in the center. To assume that bodies exhibiting the glycogen reaction be nothing else than glycogen, would be equally erroneous as to class them as "merely fat droplets," because they behave in a similar manner.

Mencl (1910) preferred to interpret the brown color, caused by iodine in buds of Azotobacter, as indicating amyloid, and rejected the assumption that they are plasmatic substances.

The coccoid bodies of sulphur bacteria, whose motility and multiplication had been studied by *Zopf*, were claimed by *Winogradsky* (1888) to be nothing else than "sulphur granules," an assertion which has been sufficiently answered by *Zopf* (1895). Concerning the blastia of *Perty* (1852), *Migula* (1897, Vol. I, p. 8) made an analogous, equally unfounded statement.

The "Schwebekörper" or "Aërosomen," attributed by *Molisch* (1907) to Rhodobacteria and Phycochromaceae, will also have to await renewed critical study.

The astonishing properties of the "vacuoles," discovered by *Zettnow* (1896–1897) inside, as well as outside, of various spirilla, have been mentioned on page 99; and the interesting interpretation given by *Hest* (1907) in regard to the "pseudo-vacuoles" of yeast cells, was quoted on page 109. *A. Fischer* (1903, p. 7) was of the opinion that deeply staining inclusions in spirilla were to be explained as vacuoles, wherein the stain became accumulated, while other investigators usually have interpreted those parts of the body to be vacuoles, which were only weakly stained or not at all.

Some special rôle in oxydative processes going on in the cell has been attributed to granules present within the bacterial cells by *Dietrich* and *Liebermeister* (1902), as well as by *Brandt* (1913). If this hypothesis should be correct, the fact itself would not militate against an eventual participating of such granules in the processes of multiplication and reproduction.

All cell inclusions mentioned above, part of which will undoubtedly be recognized as identical with gonidia or with regenerative bodies, when thoroughly studied, have been classed as the result of either the normal or the abnormal metabolism of the cell. The "fatty degeneration" especially plays a conspicuous rôle with many authors, despite the rather insufficient basis on which this hypothesis rests. There are numerous other cases, however, where it also has been considered to be quite sufficient, simply to state that the objects seen were "merely involution forms," and to abandon all further research upon them. With regard to the vegetative cells it has been shown in the first chapter (pp. 24–29) to what extent this term has been misused very frequently, so that it is not necessary to dwell upon this point once more. Only this may be emphasized again, that among the reproductive organs the endospores most clearly display all marks of true involution, but they hardly ever have been classed as such. They too show, however, that as in many other cases, so also here, involution may be followed by evolution, and the same holds true for bacterial reproductive organs generally. That, for instance, the sporoid bodies in vibrios and spirilla should not be laid aside as "involution forms," as was done by *Doyen* (1885) and others, has been pointed out by *Weibel* as early as in 1888. He says directly:

Es bedarf fast einer gewissen Selbstüberwindung, sie als Sporen zu verleugnen.

That the exceptional resistance, often, though not always, exhibited by endospores, is not to be found with the other reproductive organs, has evidently also caused some misunderstanding. *Woodhead* (1891), for instance, makes the following remark concerning the so-called arthrospores of the cholera bacillus, notwithstanding their ability to germinate:

As any apparent spores that have been formed invariably failed to resist the action of drying, such "arthrospores" containing bacilli must, for the present, be looked upon as involution forms.

The same standpoint was taken more recently by *Hiss* and *Zinsser* (1914, p. 16), as well as by *Kendall* (1916, p. 30). *Wertheim* (1899), who first observed the breaking up of the Gonococcus into minute coccoid bodies, was careful enough to test their further behavior and was able, therefore, to find out that also in this case the "involution" was followed by a new evolution of typical cocci. *Swellengrebel* (1907), on the other hand, classed and discarded the round bodies within spirochaets as "involution forms," though he saw them growing and noticed their "very complicated inner structure," both undoubtedly no marks of degeneration. With regard to the "conidia" (i. e., gonidia and regenerative bodies) described by *Almquist, Gotschlich* (1909) made the unique remark that they can not be accepted as reproductive organs, because they do not have "einen bestimmten, streng eingehaltenen morphologischen Character"; an interesting proof to what extremes an author may be misled by strict adherence to the monomorphistic doctrine. That the German author, in fact, erred in making this statement, is sufficiently proven by an inspection of *Almquist's* drawings, reproduced as figure 54 on Plate N, and of his photographs, to be found on Plate XI as figures 135–139. The form of these reproductive organs is at least as distinct as that of the vegetative cells, and it has been emphasized already that especially the round regenerative bodies of very different species may assume a vexatiously uniform appearance. But even if *Gotschlich's* claim would be right, his remark would still have to be rejected, because the true character of a reproductive organ is always determined by its physiological behavior, viz., by its ability to reproduce vegetive cells, but never by its morphology.

The term "granular decomposition" has been often used as affording another chance to bring bacteriological researches to an early end. The process was described by *Hueppe* (1886, p. 108) as "retrograde metamorphosis"; the granules were declared by him to be entirely unable to enter on a new development, and it was pointed out by him specifically that they should not be put parallel to gonidia. Less dogmatic, but more correct, *Cornil* and *Babes* wrote in their textbook (1890, Vol. I, p. 33):

On peut constater, à un moment donné dans la chambre humide, que des bactéries de diverses espèces se transforment en granulations qui resemblent à des microbes ronds. Mais souvent ces granulations ne sont plus vivantes ni inoculables.

The experiments made by *Pfeiffer* (1894) and by *Pfeiffer* and *Kolle* (1896) upon the granular decomposition of cholera and typhoid bacilli in immunized guinea pigs, as well as those of *Emmerich* and *Saida* (1900) upon the analogous behavior of anthrax bacilli, when treated with pyocyanase, have especially created the widespread belief that all "granular decomposition" without exception be indicative of the death of the bacteria. However, already in 1898 *Cantacuzène* pointed out that the granules in *Pfeiffer's* experiment are, at least sometimes, living and able to propagate; and he also discovered the interesting fact that only living, not dead, organisms showed this kind of transformation. Bacilli killed by heating were still agglutinated within the animal, but were otherwise unchanged after 3–4 hours. *Kohlbrugge* (1901 *a*) noticed that hemoglobin stimulated the granular transformation of *V. cholerae*, and he also observed the reproduction of regular bacilli from these granules. *Gotschlich* (1903, p. 58), too, admits—

dass die sonderbaren körnigen Degenerationsproducte der Cholerabacillen beim Pfeifferschen Phänomen, sowie der Pestbacillen in Bubonen . . . eine Zeit lang ihre Lebens- und Regenerationsfähigkeiten in Kulturen behalten.

That the same may not only happen in cultures but also in the organism, was indicated by an observation made by *Nakayama* (1906) in animal tests with Actinomyces asteroides, where a new growth of threads started from the granular detritus within the phagocyts. *Much* (1909) emphasizes with regard to the dissolution of bacteria within the leucocyts:

Auflösung ist nicht gleichbedeutend mit Abtötung . . . Bringt man Pneumokokken mit einem agglutinierenden Serum in Berührung, so quellen sie auf und verlieren volkommen ihre Färbbarkeit. Trotzdem sind sie aber nicht abgetötet.

The breaking up of *Spirochaeta gallinarum* into granules, when kept in fowl's blood, is another instance where granular decomposition does not mean that life is at its end. According to investigations made by *Hindle* (1911) and others, these granules are undoubtedly reproductive organs, though *Swellengrebel* (1912) tried to apply the volutin hypothesis in this case, too.

A very thorough discussion of the whole subject has been published by *Herzog* (1913), who once more confirmed that "granular decomposition" and "partial bacteriolysis" of gonococci, plague, cholera, hog cholera, and other pathogenic bacilli within the body is by no means always equivalent to their ultimate destruction; the granules are eventually able to reproduce a new generation of typical bacteria. It may be added that *Simonini's* (1914–15) studies upon the influence of certain elements (lantham, cer, thorium) upon *B. coli, typhi, dysenteriae, cholerae, subtilis, anthracis, diphtheriae*, meningococci, gonococci, etc., have also furnished several interesting details, which may become helpful for further work upon the meaning of this "granular decomposition." Here the granules once more have proved themselves to be able to act as reproductive organs, though the process of regeneration was often greatly delayed, and not infrequently such properties as virulence, motility, gelatine liquefaction, were absent for a long time in the new cultures, developed from the granules.

Closely related to the facts just mentioned are other observations like those recorded in 1881 by *Fokker* and in 1883 by *Archangelski* concerning the temporary replacement of anthrax bacilli by coccoid bodies within the organism. *Vignal* (1889) noticed that in artificial cultures, too, and already from the second day on, some of the rods of *B. mesentericus* began to contract their plasmatic content into similar granules, leaving vacuoles in the cells, which fact was interpreted by the French author as follows:

Il est impossible d'attribuer cet état à un appauvrissement du milieu nutritif ou à la formation de matières nuisibles, car à côté des bacilles vacuolisés on en trouve d'autres qui se divisent énergiquement.

Many authors, however, were only too willing to declare a priori any formation of granules to be degenerative, while only few were inclined to admit that degeneration might be followed by regeneration and both processes are part of the normal life cycles of the bacteria.

The following remark made by *Chester* (1901, p. 14) with regard to the granules in Mycobacteria, which he already correctly classed as gonidia, holds true for many analogous cases:

Certain bacteriologists have considered many of these so-called gonidia as degeneration forms; but it is more likely that they are distinct morphologic elements, inasmuch as degenerative elements could not be expected to produce new vegetative cells.

On the other hand, it was a fundamental mistake when *Wladimiroff* (1903 *b*) declared the granules in spirochaets to be merely degenerative, "because" they are not resistant against heating. *Gotschlich* (1903, p. 43), *Kruse* (1910, p. 31), as well as *Lehmann* and *Neumann* (1912, p. 517), also classify this granula formation as "degeneration," though they admit at least the possibility of a succeeding regeneration.

The terms "segmentation" and "fragmentation" have been used occasionally, especially in regard to the formation of arthrospores by Actinomycetes. *Kruse* (1896 *a*, p. 55) wanted to have both terms sharply separated:

> Nicht zu verwechseln mit der Segmentierung, durch welche lebensfähige, normale Elemente geschaffen werden, ist der unregelmässige Zerfall von kürzeren und längeren Bakterienzellen in ungleiche und oft abnorm gebildete Teilstücke, die Fragmentierung, die in alten Kulturen zu beobachten ist.

But he defined himself the fragmentation in the following manner:

> Es ist das offenbar ein regressiver Vorgang, der hier nur erwähnt sein mag, weil die Möglichkeit nicht ausgeschlossen werden kann, dass unter günstigen Umständen aus dem Zerfall noch lebensfähige Keime hervorgehen, die sich durch eine Art von Ver jüngungsprozess . . . zu normalen Elementen regenerieren können.

Both processes, therefore, are reproductive; and already *Zopf* (1883, pp. 10–12) has described the fragmentation of bacteria as "some kind of propagation," placing it parallel to the production of the so-called hormogonia by fission-algae. Accordingly, both terms have been used in the bacteriological literature, especially in papers on Actinomycetes, practically synonymously, as may be seen from the publications by *Lachner-Sandoval* (1898), *Neukirch* (1902), *Gilbert* (1904), *Lepeschkin* (1904), *Haas* (1905), *Schütze* (1908), and *Lehmann* and *Neumann* (1912, p. 623).

Růžička (1907) has correctly emphasized that the regeneration of normal bacteria from living fragments has so far not met with adequate attention, despite the important rôle played by the analogous process in the life of other primitive plants and animals.

In the same manner as the terms "degeneration," "involution," "reserve material" or other "cell inclusions" had to serve undoubtedly much too frequently for "explaining" the observations made upon various types of reproductive organs and for uniting them with the rigid monomorphistic doctrine, which allowed only one constant form of the vegetative cell and only one mode of reproductive organ, the endospore, as studied by *R. Koch* and his pupils, so also the genuine or merely hypothetical artefacts have been often invoked to allow a quick discarding of unexpected facts.

Among the so-called artefacts those introduced by *A. Fischer* (1891, 1900) as being the products of plasmolysis and plasmoptysis have been widely accepted by bacteriologists as really important facts. Though *A. Fischer's* claims were supported by only very little and obviously unsatisfactory experimental work, and though only very few confirmative, but many contradictory, results have been recorded since then, especially the plasmoptysis, characterized by *A. Meyer* already in 1905 as an "outgrowth of *A. Fischer's* vivid imagination," is still treated by writers of bacteriological textbooks as a very important fact. There is no doubt, of course, that bacteria like other cells may be induced by a hyperosmotic environment to contract their cell plasma, i. e. to exhibit so-called plasmolysis; and it is equally beyond question, that a sudden change from high to low pressure may cause an increase of the inner tension to such an extent, that the cell wall breaks and part of the content is forced out with more or less vigor. *A Fischer* (1900) himself, however, has practically eliminated this osmotic basis of his theory by reporting first that plasmoptysis may occur with some but not with all cells, when they are transferred from a low to a high concentration, and, second, that plasmolysis and plasmoptysis may occur simultaneously in the same single cell (*A. Fischer,* 1900, p. 10). Accordingly, *Kolle* and *Hetsch* (1911, p. 30) readily accept both terms as correct explanations of all kinds of processes going on in cultures, as well as in the organism, which they consider to be degenerative, and state explicitly:

> Die Ursachen der Plasmoptyse und Plasmolyse können sehr verschiedenartig sein . . . Es ist daher nicht erlaubt, aus dem Vorgang selbst Schlüsse auf das auslösende Agens zu ziehen.

If every plasma contraction should be called plasmolysis, then naturally all gonidia formation would have to be identified with it, but as the term can be used correctly only in those cases where, in fact, the change in osmotic pressure acts as causative agent, gonidia formation may occasionally be mistaken for plasmolysis, especially if the last-named authors' advice should be accepted, but more careful research will always reveal the inherent difference between both processes. *Podwyssotzky* and *Taranoukhine* (1898) went even so far as to link the spore formation of *B. anthracis* with *A. Fischer's* plasmolysis theory, though this species, like several other spore-forming bacilli, was declared by *A. Fischer* (1903, p. 25) to be not subject to plasmolysis on account of its permeability. As many other species (sarcinae, streptococci, staphylococci, etc.) were also found by the same author to be not inclined to show any plasmolytic reaction, this process unquestionably can not be used as a correct explanation for the formation of those granules by all bacteria, which, though contracted plasma, demonstrate by their further behavior that they are actually reproductive organs.

That genuine plasmoptysis has still less to do with the production of reproductive organs than has plasmolysis, is equally evident. *A. Fischer* never furnished photographic pictures of what he saw in his experiments; the drawing reproduced as figure 62 on Plate O from his textbook (1903, original fig. 27) is obviously highly schematized and is rather different from the drawings given in another paper (1906), one of which has been reproduced as figure 181 on Plate XV (from original fig. 8 on Pl. III). This ejecting and dissolving of irregular clumps of plasma is, indeed, what might be expected, and is also in accordance with the original description given by *Fischer* (1900), while all his other data concerning the formation of a new membrane around the ejected plasma and the motility of these bodies, evoke a strong suspicion, that he actually has had side by side in his preparates plasmoptysis, as well as gonidia and regenerative bodies, and that indiscriminate "explaining" of the latter fact by the former has caused the development of his incorrect theory. Furthermore, it has to be remembered, that many of the globules, considered by *A. Fischer* to be "Plasmoptyse-Kugeln," have been merely droplets of some organic substances ("dirt droplets," as *A. Meyer* called them), which are indeed quite common with coverglasses which have not been thoroughly cleaned. *Leuchs* (1905) has directed the attention to this fact, which has been admitted by *A. Fischer* (1906). Additional data concerning genuine and so-called plasmoptysis were furnished by *Blau* (1905), *A. Meyer* (1905–1906), *Hammerl* (1906) and *Garbowski* (1906–1907). The last-named author, though working in *A. Fischer's* own laboratory, was equally unable to confirm this authors statements. A fairly pronounced plasmoptysis was recorded only by *Schuster* (1910), who cultivated some bacteria in a 10 per cent ammonium sulphate solution. Under normal conditions plasmoptysis is of no importance whatever; a study of the slow growth of budding gonidia and regenerative bodies will, as *Meirowsky* (1914) has emphasized, at once demonstrate that these organs are by no means the result of a sudden osmotic eruption, and their further behavior confirms this fact.

The occurrence of artefacts in stained preparations is a point which needs constant attention in all investigations upon gonidia and regenerative bodies. Very deceptive artefacts may be obtained occasionally with nutrient solutions containing albuminous or fatty substances or with certain staining methods; but it would be wrong, of course, to conclude from such happenings that the same artefacts are also present in other cases. Important information in this respect may be derived from *A. Fischer's* book entitled "Fixierung, Färbung and Bau des Protoplasmas" (1899), though again the conclusions drawn by the author are often out of all proportion to their experimental basis. *Weibel* (1888), who was among the first to study formation and development of bacterial regenerative bodies, has already selected the one way which avoids the disturbing influence of artefacts in stained preparations, viz., the examination of the living organism in the hanging drop. That vital staining with methylen blue may be helpful, was shown by *Zettnow* (1897), *Nakanishi* (1900*a*), *Růžička* (1903), *Meirowsky* (1914*b*), and others. Absolutely clean coverglasses are, of course, equally important in this case, as they are in regard to "plasmoptysis."

A particularly disturbing effect may be caused occasionally, as was pointed out in our second preliminary report (*Löhnis* and *Smith*, 1916*b*), by the fact that many of the thick walled regenerative bodies are killed, but not dissolved by thorough heating of the substrates. Therefore, it may and will happen, especially with substrates containing pepton or other ingredients which were exposed to strong bacterial infection, that dead foreign bodies are present in perfectly prepared and sterilized media, which may enter the field, well stained and evidently being genuine regenerative bodies, though actually representing an unwelcome contamination. The use of various substrates, kept in thoroughly cleaned vessels, will usually suffice to eliminate this possible cause of error, though occasionally filtering of the medium through a reliable bacteria filter will become necessary to secure definite results.

Granules in blood and tissue may be easily mistaken for reproductive organs of bacteria and vice versa. The granules in "Mastzellen" have been discussed on p. 111. That those in liver and other tissue may be bacterial gonidia has been mentioned repeatedly (see e. g. *Bordoni-Uffreduzzi*, p. 97, and *M. E. Abbott*, p. 103). The production of "infective granules" by spirochaets has directed the attention of bacteriologists to the hemoconia and other granules in blood. As early as in 1880 *M. Wolff* and *Guttmann* have dwelled upon this subject, which has been more recently discussed by *Rabinowitsch* (1909), *Balfour* (1911*c* and 1912), *Gleitsmann* (1913), *Herzog* (1913), and by *King*, *Baeslack* and *Hoffmann* (1913). As with blood, the dark field method may also cause considerable trouble when used in other cases; comparative examinations of the sterile media are necessary to avoid mistakes due to the presence of other granules in the substrates.

Cienkowski already emphasized in 1877 that the direct observation of the development of gonidia to bacteria is the only final proof that these small round bodies are not merely cell inclusions, but actually reproductive organs. *Zopf* (1879), *Toussaint* (1884), and other early authors took the same standpoint, which, of course, is beyond dispute.

But *Zopf* (1895) was also right when he refuted *Winogradsky's* exaggerations concerning the identity of gonidia with "sulphur granules" on the ground that he had seen them multiply as such, though they did not revert in his experiments into the original rods and threads. At the present time, where so little is known upon the conditions favoring the upgrowth of gonidia and regenerative bodies to fully developed bacteria, it will have to be considered to be, indeed, quite satisfactory, if only the formation and the multiplication of these reproductive organs as such can be directly followed. *Adami*, *Abbott*, and *Nicholson* (1899), for instance, were not always able to get a regular upgrowth from the gonidia of *B. coli;* sometimes they reverted promptly, in other cases they merely multiplied. A culture of motile "cocci" (gonidia), isolated by *Stamm* (1914) from *V. cholerae*, which was shown in figure 82 on Plate VII, grew as such in 65 transfers during 7 months, then it reproduced again large curved forms. Similar results will have to be expected frequently, but they can at least be accepted as decisive answer in regard to the various problems concerning artefacts, reserve material, etc., though, of course, the possibility of a contamination by cocci has also to be kept in mind. This point, however, can be eliminated without great difficulty. Microscopically, as well as macroscopically, the growth of gonidia and regenerative bodies is so different from that of micrococci, that a somewhat experienced investigator will not be led astray.

The situation is much less satisfactory if the problematic bodies refuse to grow under the conditions selected for the experiments. Such negative findings have been recorded, e. g., by *Růžička* (1907), *Fontes* (1910), *Leishman* (1910), *Th. Smith* (1913), *Wolbach* (1915), and many others. *Leishman* and *Smith*, however, though failing in the cultural experiment, succeeded in the animal test, and there is no doubt that as our knowledge will increase also cultural experiments will become more and more successful. To specify the conditions beforehand and, if they prove to be not suitable, to draw from such a negative result the final conclusion that no growth is possible, is, of course, a very serious, though unfortunately not infrequent, mistake. *Miehe* (1913), for instance, was absolutely certain that the globular forms produced by his *B. repens* were "merely involution forms," because they did not germinate in his hanging drop. But the normal rods of *B. foliicola*, which he also studied in the hanging

drop, were equally not inclined to grow and to multiply under his eyes; yet there is nothing said about their being "merely involution forms." With endospores the irregularities in germination are well known, and in this case a negative finding will never be accepted as decisive. Exactly the same standpoint has to be taken in regard to the other reproductive organs of the bacteria.

The motility often shown by the gonidia, and sometimes by regenerative bodies, as well, may be accepted as a fairly conclusive proof, though the Brownian movement of small foreign bodies, especially conspicuous in the dark field, makes "eternal vigilance" imperative. The use of antiseptic substances was found to be helpful by *Kuntze* (1904). The staining of flagella is still more conclusive, but, of course, also much more difficult. The photographs reproduced as figures 160 and 161 on Plate XII, show clearly that satisfactory pictures of these minute details are not easily obtainable. One long flagellum seems to be very common with the motile gonidia of practically all groups of bacteria. It has been so recorded by *Giard* (1882) for *Crenothrix*, by *Beijerinck* (1888) for *B. radicicola*, by *Plaut* (1907) for *B. fusiformis*, by *D. H. Jones* (1913) for *Azotobacter*, by *Marrassini* (1913) for *B. subtilis*, and by *Stamm* (1914) for *V. cholerae*. As is the case with the motility of the bacilli themselves, so also the motility of these reproductive organs may vary according to circumstances. According to *Migula* (1897, Vol. I, pp. 202–205) the gonidia of Crenothrix are immotile, while others saw motility, and Cladothrix gave him immotile as well as motile gonidia. *Adami* and his collaborators (1899) found those of *B. coli* immotile, while *Kellerman* and *Scales* (1916) noticed a very conspicuous motility. The gonidia and regenerative bodies of *V. cholerae*, which practically always exhibit a lively motility, as was seen by *Hammerl* (1906), *Kolle* and *Hetsch* (1911), *Stamm* (1914), and others, may show variation, too; *Almquist* (1908) found them to be motile at 20° C., immotile at 10° C.

(c) THE DIFFERENT TYPES OF REPRODUCTIVE ORGANS.

It goes without saying that a sharp distinction between the different types of reproductive organs is not possible in every case. They all serve the same fundamental purpose: cell reproduction; but in addition they may either participate in multiplication, or they may act as more or less resistant resting forms, or they may combine these two supplementary functions. Their formation, development, and character will differ accordingly, but some overlapping will also be noticeable. Minute spots of nuclear material represent the beginning of all reproductive organs; the addition of plasmatic substances, of reserve material, and of a more or less resistant membrane determine their final appearance; but though this will suffice for making a correct classification in most cases, sometimes a close study of the actual development of the bodies concerned will be necessary to distinguish correctly, for instance, between regenerative body, arthrospore, and microcyst, or between endo- and exospore.

The names used by us at present for the four groups of reproductive organs are:

(1) Gonidia.
(2) Regenerative bodies and exospores.
(3) Endospores.
(4) Arthrospores and microcysts.

The meaning of these terms, and why they have been selected, may be discussed first; the literature relating to character and behavior of the different types of reproductive organs will be reviewed afterwards.

What we call gonidia of the bacteria is probably identical, at least partially, with what has been called eggs ("Eier") of the bacteria by *Ehrenberg* (1838); some of his observations, however, may also relate to endospores, and the name itself would be, of course, unacceptable now. The term "blastia" used by *Perty* (1852) is much better, but its original meaning has also been too broad. The endospores have been kept separate by the Swiss author, but besides the bacterial gonidia, his blastia also enclose regenerative bodies of the bacteria and various reproductive organs of protozoa. The "micro-gonidia," which *Karsten* (1869) observed to grow up to bacteria, have been probably also gonidia, as well as regenerative bodies. In relation to Crenothrix *F. Cohn* (1870) made use of the terms micro- and macro-gonidia, though he

admitted that no sharp distinction between both can be made. According to our present arrangement his macro-gonidia would have to be classed among regenerative bodies or microcysts. What *Sachs* (1875) named swarm-spores or zoospores of lower algae is equivalent to our gonidia of the bacteria; he calls them also micro- and macro-gonidia. In *Zopf's* paper on Crenothrix (1879) the terms gonidia and spores are used synonymously. According to *Béchamp's* description (1883) some of his "microzymas" are undoubtedly identical with the bacterial gonidia, but it is equally obvious that many other things, even part of the bacteria themselves, would be covered by the same name. Much of what should have been termed gonidia, has been called "cocci" by *Zopf* (1883); an inaccuracy which has been justly criticized by *Hueppe* (1886). Unfortunately, this author erred by asserting that gonidia be resting forms and unable to multiply as such, the latter fact being characteristic for cocci. If this would be true, *Zopf*, not *Hueppe*, would have been right.

The application of the term gonidia to the club-shaped cells of Actinomyces and of other organisms, as was done by *Bollinger* (1877) and by *A. Neisser* (1888), can also not be accepted as correct. These cells may contain gonidia, but they are not gonidia (i. e., seed) themselves. What *Klebs* (1887) called "microsomes" of the bacteria have been evidently true gonidia, and this term might be used had it not been applied by other writers, e. g., by *Spencer* (1898, p. 253), in a much more general sense to all plasmatic granules to be found in the cells. The motile gonidia of *B. radicicola* have been called zoospores by *Atkinson* (1893) and by *Hartleb* (1900). *Thiercelin* (1903) chose the designation "microblastes" for the gonidia of his Enterococcus. The so-called spores of *Spirillum endoparagogicum* (*Sorokin*, 1887), *Actinomyces bovis* (*Bostroem*, 1890), *B. coli* and *typhi* (*Almquist*, 1893), *B. fusiformis* (*Tunnicliff*, 1906), and of *Leptothrix* (*Chlamydothrix*) *ochracea* (*Petschenko*, 1916) exhibit all marks of genuine gonidia. Those produced by the trichobacteria have been called by *Migula* first (1900) conidia, later (1904) gonidia. *Ellis* (1907) and *Benecke* (1912) also wrote upon "conidia" in trichobacteria, while *Chester* (1901), *Schmidt* and *Weis* (1902), as well as *Frost* and *McCampbell* (1910), gave preference to the term "gonidia." The so-called conidia of *Almquist* (1904–1917) include gonidia as well as regenerative bodies. Whether the "sporoids" of *Růžička* (1909) have been gonidia must be left undecided. What *Jones* (1913) described as "gonidia spores" of Azotobacter, however, have been undoubtedly true motile gonidia. The expression "infective granule," used by *Balfour* (1911–1913) and others in relation to the gonidia of spirochaets, as well as other protozoological terms, like "marginal points," "anaplasma," are evidently not preferable to the old, fairly well established and defined term "gonidia." The terms blastia, microblasts, etc., I believe, do not deserve preference. As not all gonidia are motile, the use of the name zoospores can also not be recommended. And the rather indefinite expression "spores" should certainly be avoided. That "gonidia" (derived from γόνος = offspring) should not be associated with or replaced by "conidia" (derived from κόνια = dust) needs hardly to be emphasized. Conidia are, according to *Lindau* (1904, p. 191):

> Sporen, welche exogen, d. h. ausserhalb der Zelle durch Abschnürung entstehen.

And:

> Die Konidien sind die recht eigentlichen Fortpflanzungszellen des Pilzreiches, denn sie zeigen die Anpassung der Pilze an das Landleben in der höchsten Form.

It is true that under abnormal conditions conidia may be also formed internally, as has been described, for instance, by *Klöcker* and *Schiönning* (1899) for *Dematium pullulans* and other fungi, and one might say that the arthrospores produced by Actinomyces at its aerial hyphae are genuine conidia and the gonidia formed within its cells are such abnormal endogenous conidia. However, it seems to be much more preferable and recommendable to avoid, as far as bacteria are concerned, the term conidia entirely and to speak alone of gonidia. With the trichobacteria the latter term has been applied by some authors also to full-grown cells, when these are formed within the sheath, an extension of its original meaning, which better will be avoided as far as possible.

According to the old definition, given by *Sachs* (1875, p. 211) with regard to the lower algae, which, however, is equally applicable to the bacteria, gonidia are organs of asexual repro-

duction, formed by the contraction of the plasmatic cell content, which leave the parent cell either by breaking the cell wall, or which become liberated when the cell dissolves. Motility is frequently, though not generally, noticeable with bacterial gonidia. Usually two, four, or more gonidia are formed within the same cell. Their resistance, as a rule, is not very different from that of the full-grown, vegetative cell, as they are serving much more for multiplication than for preserving the life under unsuitable circumstances. They often seem to be made up nearly exclusively of chromatin substances; occasionally, however, the presence of reserve material (fat, starch, glycogen, etc.) may become so conspicuous that errors in the microchemical analysis may be caused.

As was mentioned above, the so-called infective granules, marginal points, etc., of protozoa are very similar to bacterial gonidia. What *Minchin* (1915) said in regard to protozoa holds also true in our case:

> Infective granules are true endogenous chromidial buds.

And:

> Each bud, when complete, has the morphological and cytological value of a true cell, very minute in size and reduced almost entirely to its chromatin elements.

That the bacterial gonidia sometimes may multiply as such for a long time before they revert to normal cells is in good agreement with this view.

Sometimes the endogenous production of gonidia assumes such proportions that a considerable increase in size and an alteration in the shape of the parent cell becomes visible. *Toussaint* called such cells "sporangia" (according to *Magnin* and *Sternberg*, 1884, p. 150) or "pseudothèques" (according to *Rodet*, 1894, p. 117). *Finkler* and *Prior* called them first "Ammen" (1884), later "Keulen" (1885). *Artigalas* (1885) spoke of "spores" containing "sporules," and *Carpano* (1913) also used the term "spores." That the latter term should not be applied in this manner is beyond question. But the names used by *Finkler* and *Prior*, as well as by *Toussaint*, are equally not acceptable. Therefore, it seems best to introduce the term "gonidangium," already used in mycology, but to reserve it for those "giant cells" producing numerous gonidia, and not to apply it to normal cells containing a few gonidia, though this, of course, would be etymologically equally correct. As will be seen, very many of the so-called involution forms of spherical, pear, and club shape are, in fact, gonidangia.

What we now call "regenerative bodies" is a collection of different reproductive organs whose proper separation and classification must be left for the time when more data will be available. Among the reproductive organs as described by earlier authors the following may have been regenerative bodies: Some of the macro-gonidia of *F. Cohn* (1870), the "arthrospores" of *V. cholerae* as described by *Hueppe* (1885), the round reproductive organs of Actinomyces growing singly on short side branches, which were called "chlamydospores" by *Schürmayer* (1900), some of the "bacteroids" of the nodule organism and of other bacteria, the "zygospores" of *B. radicicola* studied by *Hartleb* (1900), the "zygo- or stylo-spores" of *B. tuberculosis* described by *Droba* (1901), the "Dauerkapseln" of *B. tuberculosis* mentioned by *Schroen* (1904), part of the "conidia" of *Almquist* (1904–1917), probably some of the "unreife Sporenanlagen" frequently found by *Grassberger* (1903) with anaerobic bacilli, and the "Regenerationsformen" of Azotobacter discovered by *Prazmowski* (1912, p. 145).

Generally the regenerative bodies are characterized by their being easily and deeply stained by aqueous dyes, by their different appearance as compared with the vegetative cells (globular, oval, or irregular), by their ability to reproduce normal cells immediately or after having propagated as such by fission or by budding, by their distinctly increased resistance against drying, heat, or other detrimental influences. But, as has been said above, this grouping can be only accepted as some temporary arrangement, which will have to be discarded as soon as the different components of this group will be more completely known.

Some of them are evidently related to what we call terminal exospores and probably will later have to be united with them. Others seem to be genuine zygospores, as will be discussed more fully in Chapter IV. Many of the round forms, as well as some of those of irregular shape, usually characterized by an especially solid appearance, are produced directly

from the symplasm, as will be demonstrated in Chapter III. Perhaps the name "sclerotia" might recommend itself for the latter forms. But all final action upon this point, as well as the proper naming of the remaining "regenerative bodies," must be left to future experimental investigations.

"Exospores" are those reproductive organs which are produced either terminally or laterally and whose staining reaction and resistance are similar to those of the endospores. As to their mode of being formed, it seems not improbable, that they, too, are zygospores, and perhaps this will be their final denomination.

At present it is customary to call the "endospores" of the bacteria simply "spores", but this custom will have to be abandoned, as it is beyond doubt, that other bacterial reproductive organs are equally true "spores." The demand of some authors, like *Gamaleia* (1888), *Bruns* (1895), *Hawthorn* (1903), *Mertens* (1903), *Frost* and *McCampbell* (1910), that only those reproductive organs should be called spores, which are characterized by their special staining reaction and their exceptional heat resistance, can not be accepted as being correct. Σπορά means "seed," and therefore even the gonidia might be called spores, as has been done, indeed, by several authors. But as their morphological, as well as their physiological, character is so widely different from that of the typical spores, undoubtedly a special name was preferable in that case. On the other hand, it seems not to be justified to confine this term strictly to only one type of reproductive organs, and to exclude all others, which according to formation, development and general character, are very similar to them, though not quite so resistant to staining and heating. The use of the distinct term "endospore," therefore, is to be recommended; the term "cyst," as used by *Gamaleia* (1900), on the other hand, should not find application in this case.

The term "arthrospore," introduced by *Caspary* into the mycological literature, has been refuted by *Bail* as early as in 1857 on the ground that only those reproductive organs should be called spores which are the results of some process of fructification. The opposition was still more pronounced after *De Bary* (1884) had taken up this term for bacterial reproductive organs and *Hueppe* (1886), as well as *De Toni* and *Trevisan* (1889), had accepted and extended its use. *Kruse* (1896 *a*, p. 60), *Migula* (1897, Vol. I, pp. 37, 168; 1900, p. 8; 1904, p. 123), *Schmidt* and *Weis* (1902, p. 58), *A. Fischer* (1903, p. 42), *Gotschlich* (1903, pp. 82, 83), *Muir* and *Ritchie* (1903, p. 8), *Günther* (1906, p.21), as well as *Hiss* and *Zinsser* (1914, p.16), have all taken a more or less pronounced stand against this theory. However, a careful study of all reports concerned leaves no doubt, that the special morphology, increased resistance, and the germination of these spores have been fully ascertained at least in some cases, and, therefore, it is not admissible to discard them lightly as being "simply involution forms," as was done repeatedly. The term has been fairly correctly used by *G. M. Sternberg* (1893, p. 17), *Crookshank* (1896, p. 19), *Lafar* (1897, p. 62), *Gamaleia* (1900, p. 17), and *Benecke* (1912, p. 179), though all these authors paid more attention to those cases, where the whole vegetative cell was transformed, than to the others, where by a preliminary segmentation joints were formed which then became arthrospores. In our first preliminary paper (*Löhnis* and *Smith*, 1916 *a*, p. 679, footnote) we also said:

> We think it best to reserve the name "arthrospore" exclusively for those cases where the whole cell acquires the character of a spore.

However, a more thorough consideration of the problem has made the conclusion inevitable, that whole cells turning into resting forms should be named "microcysts," and the term "arthrospore" should be used for those spores which "like a chain of beads are formed by fission" according to *Jackson's* definition (given in his Glossary of Botanic Terms), which also agrees best with the etymology of the term, viz: τὸ ἄρθρον = the joint. It has been mentioned before that in this way the term "conidia," sometimes used for the aerial spores of Actinomyces, can be avoided, which is very desirable on account of its being frequently misused and also easily mistaken for "gonidia." If these reproductive organs of Actinomyces are accepted as type of arthrospores, their being produced by segmentation or fragmentation, their increased resistance, as well as their germination, can all be accepted as thoroughly studied by various investigators. Whether some process of fructification precedes the formation of these spores, must be left in

doubt at present, in the same manner as with regard to the endospores. That other bacteria are able to produce such arthrospores is beyond question. Those of the Proteus group are most generally known, but others formed by saprophytic spirochaets are also quite typical, as may be seen from the drawings made by *Gross* (1912, original figs. 8 and 9), which were reproduced as figure 63 on Plate O.

If the whole cell becomes more resistant by thickening its membrane, and sometimes also by reducing the amount of water present within the cell, the resting form produced may be termed "microcyst." The analogous cells of Nostoc have been called "heterocysts" by *Sachs* (1875, p. 215), those of Leuconostoc by *Van Tieghem* first "spores" (1879*c*), later "kystes" (1884, pp. 1105, 1108), and those of several spore-forming bacilli "chlamydospores" by *A. Meyer* (1901*b*), whose drawings, reproduced as figure 64 on Plate O (from original figs. 4 and 15 on Pl. XX), illustrate the difference of the microcysts when compared with *Gross's* picture of the arthrospores of spirochaets. The "spores" of Myxococcus exhibit also more the character of microcysts than that of arthrospores, though some similarities are noticeable in the latter direction, too, as may be seen from the drawing made by *Zukal* (1897), reproduced as figure 65 on Plate O (from original fig. 3).

Κυστις means cavity, bag, and a cyst is according to *Jackson* "a cell of nonsexual origin which reproduces the plant by germination after a resting period." The character of a bacterial microcyst fits this definition completely. That, however, the special name microcyst seems to be more recommendable in this case than the more general term cyst, is due to the fact, that the latter expression has been used in a different sense with the Myxobacteria, and that, as will have be shown in Chapter III, similar large cysts, i. e. "macrocysts," may also be formed by all bacteria when in the symplastic stage.

By some authors typical microcysts have been named endospores, a usage which can not be approved. *Migula* (1897, Vol. I, p. 169), for instance, insisted that *Van Tieghem's* Leuconostoc cysts had been endospores, because they had been brighter in the center and had germinated like endospores, though *Van Tieghem* clearly stated that the wall of the whole cell "se cutinise en déhors." *Prazmowski* expressed the analogous opinion in regard to resistent thickwalled cells of *Micrococcus ureae* (1888*a*) and of *Azotobacter chroococcum* (1912), despite the fact that the typical character of microcysts is especially noticeable in these cases.

The coiled and "encysted" spirochaets furnish another good example of the mode of formation of this type of reproductive organ, as well as of the correct use of the term.

That arthrospores and microcysts can not be easily distinguished when isolated is readily to be admitted. But the same holds true with regard to endo- and exospores, as well as in other cases, where the knowledge of the formation of the body in question is necessary in order to reach a scientifically correct classification.

(1) GONIDIA.

The formation of the gonidia is caused by a contraction and fragmentation of the content of the parent cell; though, naturally, the details of this process vary with the different groups of organism and to some extent with the cells themselves.

With the large trichobacteria, where *F. Cohn* (1870) first studied the formation of the gonidia, the cell content contracts itself into larger and smaller globules. When the cells break up within the sheath into 16 or more of such motile globular or ovoid granules, *Cohn* speaks of micro-gonidia; while he uses the term macro-gonidia, when only 2–4 are formed. But he himself emphasizes that both types of gonidia can not be sharply separated. The drawings made by *Billroth* (1874), which were reproduced as figure 45 on Plate L, demonstrate very clearly the characteristic formation and liberation of gonidia by some long bacilli, probably lactobacilli, as they were accumulated in whey kept at 40–45° C. The analogous description given by *Ewart* (1878) for the "sporules" of *B. anthracis,* as well as for the "bright, unusually small, almost spherical spores" of *B. termo* (fluorescens), and by *Geddes* and *Ewart* (1878) for the motile "spores" of spirilla, are also of considerable interest. A comparison of the last-named paper with those of *Perty* (1852), of *Fantham* (1911), and of *Bosanquet* (1911) leaves no

doubt that essentially the same process has been studied by all these authors (see figs. 42, 59, and 60, on Plates L and O). If the gonidia do not slip out at one end, as was sketched by *Fantham*, but are simply liberated by a complete dissolution of the cell wall, as has been observed with spirochaets, e. g., by *Bosanquet* and by *Rüther* (1910), the picture becomes very similar to what is a common occurrence with the Mycobacteria. *Lutz* (1886) made the first pictures of this process, as exhibited by *B. leprae*, reproduced as figure 36 on Plate J. Those published by *Kedrowski* (1910), reproduced as figure 37 on Plate J and as figure 153 on Plate XI, illustrate some other equally interesting phases in the formation of gonidia by this organism; they may be compared with those of the diphtheroid organism, drawn by *Babes* (1895) and reproduced as figure 34 on Plate J. The description given by *Bostroem* (1890) concerning the analogous behavior of Actinomyces also deserves our attention. The threads were seen to contain spherical, bright, "bead-like" granules, having the same diameter as the threads and being separated from each other by regular distances; they either slipped out of the sheath or became free by the dissolution of the cell wall. More recently *Hollandt* (1906) noticed that occasionally Actinomyces is able to produce micro- and macro-gonidia in the manner characteristic for Crenothrix. That the same fact can be sometimes observed with smaller bacteria, too, has been demonstrated by *Miller* (1889), when he made his drawing of the so-called *Jodococcus vaginatus*, which was reproduced as figure 52 on Plate N. *Almquist* (1893) recorded analogous findings when he studied *B. coli* and *typhi; Prazmowski* (1912) and we (*Löhnis* and *Hanzawa*, 1914; *L.* and *Smith*, 1916) saw the same facts with Azotobacter.

The sketches made by *Morck* (1891) of nodule bacteria forming gonidia, which are reproduced as figure 66 on Plate P (from original figs. III, 4, and V, 12) show an interesting ring formation, which may be found with other bacteria, too; *P. Ernst* (1902), for instance, described this fact with *B. fluorescens*. That the gonidia may arrange themselves into such a circular grouping within the parent cell, while this retains its rod-form practically unchanged, has been recorded by *Trambusti* and *Galeotti* (1892) in the case of a bacillus from water.

Usually, however, the gonidia formed by such small rods as *B. coli, fluorescens*, etc., or by the larger ones of the Subtilis-Mesentericus group, appear simply as 2, 4, or more granules, arranged in one row. A photograph of *B. coli*, made by *Kellerman* and *Scales* (1916) from a contact preparate, has been reproduced as figure 182 on Plate XV; it allows one to recognize very clearly how abundant the gonidia may already be in young colonies. According to our own observations their number usually reaches the maximum, when the development of a culture is at its height. Figure 183 on Plate XV, reproduced from our first preliminary report (*Löhnis* and *Smith*, 1916 *a*, original fig. 39), pictures this phase in the life of a spore-forming bacillus (yellow bacillus No. 41) and makes a good object for comparison with the preceding photograph of B. *coli*.

With micro- and streptococci the gonidia formation becomes most conspicuous, when these very small bodies bud out of the parent cells, but remain temporarily attached to them by a very fine, rather long stem, a peculiarity which probably has been first seen by *Thiercelin* and *Jouhaud* (1903 *a*), and which is illustrated by our photographs of *Micr. candicans, luteus*, and *Strept. lactis*, reproduced as figures 168–170 on Plate XII. But again the analogous behavior can be traced through all groups of bacteria, as was ascertained by *Meirowsky* (1914 *b*), whose most characteristic drawings have been reproduced on Plate XIV.

Data relating to the formation of a single gonidium are not available at present. Some observations reported by *Fuhrmann* (1908), *Amato* (1908) and *Růžička* (1908) indicate, however, that this process is very similar to the initial steps in the formation of an endospore.

The production of gonidangia by the bacteria is quite general. Usually they are the result of a simple swelling of the parent cell; sometimes, however, the gonidia bearing rod first forms a circle, which later develops into a large coccoid body, as has been recorded for *V. proteus* by *Firtsch* (1888), for *B. radicicola* by *Morck* (1891), and for *B. fluorescens* by *P. Ernst* (1902). This process resembles very much another one noticeable with spirochaets, where the coiled forms first produce microcysts, which then act as receptacles for the gonidia, liberated inside

by the dissolution of the coiled spirochaets. *Perrin* (1906), *Dutton* and *Todd* (1907), and others have studied this transformation. The gonidangia of spirochaets, described by *Ross* (1912) and by *Moolgavkar* (1912), seem to have been, partially at least, of the same origin. They were either "large spherical cells, studded with small chromatin granules" or more irregular, pear-shaped bodies. In figure 67 on Plate P gonidangia of *B. radicicola* are reproduced from drawings made by *Morck* (1891, original figs. 2 *b–d* on Pl. III), to demonstrate an occurrence which has been also studied by *Hartleb* (1900), *Hiltner* and *Störmer* (1903), *Rossi* (1907), *Arzberger* (1910), and others.

That numerous observations upon the formation of bacterial gonidangia were made by some of the pioneers in bacteriology at the time, when the unscientific discarding of all "involution forms" was not yet an established rule, was mentioned in the historical résumé given on pages 90–108, especially on page 100, together with a very characteristic remark made by *Migula*. The early drawings of *Billroth* (1874), reproduced as figures 44 and 45 on Plate L, are excellent illustrations of the manner in which gonidia bearing rods may develop to voluminous gonidangia. The description given by *Toussaint* of the gonidangia of *B. anthracis* is equally worth quoting. In the textbook of *Magnin* and *Sternberg* (1884, p. 150) this otherwise unpublished observation was described as follows:

> In cultivating spores of the bacteria of charbon . . . *Toussaint* has seen the filaments take a transverse diameter almost double the ordinary diameter, then the protoplasm of the filament to gather together at certain points . . . Finally the points occupied by the condensed protoplasm augment considerably in volume and form some ovoid organs, more or less elongated, or swollen into a ball, or in the form of a gourd at one extremity. In the interior of these sporangia from three to six spores afterward form, . . . finally by breaking up of the membraneous envelope the spores become free.

Still earlier findings, recorded by *Letzerich* (1876–1878) in his experimental investigations upon diphtheria and typhoid fever, are not less interesting. He saw isolated cocci in the blood grow up into large plasmatic globules, which reproduced internally new bacteria. Some sketches, published in the first paper (1876, original figs. 1–4, on Pl. XII) are reproduced as figure 68 on Plate P, because they will possibly regain new importance in further investigations upon the "coccoid" form of diphtheria, mentioned on page 79, as well as in studies upon the relations existing between Bacteriaceae and Myxobacteriaceae. At the same time *Geddes* and *Ewart* (1878) gave the analogous description of the gonidangia formed by spirilla, while *J. Israël* (1878) noticed that the club-shaped cells of Actinomyces may serve the same purpose. The pear-shaped cells were seen to break up and to liberate their granular content. Exactly the same fact has been recorded by *E. Chr. Hansen* (1879–1894) with regard to the acetic acid bacteria, whose globular forms grew up to 11μ diameter. *V. cholerae* and related organisms have also frequently exhibited their large globular or club-shaped gonidangia, which have been fairly well studied by *Finkler* and *Prior* (1884–1885), *Ferrán* (1885) *Schroen* (1886–1890), and by *Dowdeswell* (1889–1890), though they remained to *R. Koch* and his followers always uninteresting "involution forms." A reference made by *Künstler* (1885) in regard to the gonidangia of spore-forming bacilli has been cited on p. 96. It is again in complete agreement with those mentioned before. In fact, *Künstler* (1885), as well as *Schroen* (1886), have already reached the conclusion that the production of gonidangia is a common occurrence within all groups of the bacteria. More data upon this subject have been furnished by the last-named author in two other papers (*Schroen*, 1890: Zur Genese der Microorganismen, and *Schroen*, 1904: Der neue Mikrobe der Lungenphthise). Unfortunately the author seems to have been unable to finish a special publication upon "The Genesis of the Microbes," which he promised in the second paper. Concerning the tubercle bacillus he wrote in 1890 that as with the cholera vibrio so also in this case globular forms may increase in size and become "mother spores," whose content divides itself into numerous coccoid "daughter spores." And with *B. anthracis* and *Megaterium* he noticed that the normal cells swell up into large somewhat irregularly curved "Bacillen-Säckchen," containing coccoid reproductive organs, which either are liberated as such, or transform themselves already internally into new small bacilli. The dividing up of the content of such gonidangia into only two large curved bacilli has been also

recorded by *Schroen* (1890), a possibility which was mentioned by *E. Klein* (1885) and by *Dowdeswell* (1890) with regard to *V. cholerae,* and later by *Hartleb* (1900) in his studies upon *B. radicicola.*

In his last paper *Schroen* (1904) comes to the conclusion that besides the tubercle bacillus another fungus-like organism acts as causative agent of phthisis, of which he gives among others the picture reproduced as figure 192 on Plate XV (from original fig. VIII). Apparently genuine hyphae are visible in the picture. However, it is more probable that these thick threads are no hyphae at all, but slime threads very similar to those produced by *B. radicicola* and the Myxobacteria. In Chapter III this point will have to be considered more fully. The round "capsules" of *Schroen's* organism, too, seem to be clearly bacterial gonidangia. According to his own description they produce 20 to 40 thin bundles of very fine threads, which, after their liberation, appear just like tubercle bacilli. As figure 189 on Plate XV Azotobacter gonidangia have been reproduced, which were interpreted by *Beijerinck* (1901 *b*, original fig. 4) as involution forms; they make a highly interesting counterpart to the "capsules" of *Schroen's* "phthisiogenic microbe," as well as to the gonidangia of the Pneumococcus, discovered by *Artigalas* (1885) and reproduced as figure 122 on Plate X. That with the streptococci again pear-shaped gonidangia may replace these perfectly round ones, has been shown by *Maddox* (1885), who observed the liberation of the deeply staining granular content of large club-shaped cells, present within or at the end of chains of *Streptoc. lactis.* With regard to his Enterococcus, *Thiercelin* (1899) wrote:

On voit le coccus devenir très volumineux et donner naissance à un grand nombre de petits diplocoques vivement colorés au Gram, contenus dans une sorte de gangue amorphe, vaguement colorée par l'eosine.

The upgrowth of new small bacteria within the gonidangia, described by *Schroen,* has been also recorded by *Babes* (1895), whose drawings were reproduced as figure 53 on Plate N, as well as by *Gamaleia* (1900), who called these small forms "Mikromiten." That *Schmorl's* photographs of his *Streptothrix cuniculi* (*B. necroseos*), which were reproduced as figures 89 and 90 on Plate VIII, illustrate the formation of gonidia and gonidangia very well, will become apparent in this connection. *Hibler's* pictures of *B. Chauvoei,* shown on Plate X as figures 115 and 116, as well as that of *B. mallei* made by *Carpano* and reproduced as figure 96 on Plate VIII, deserve also to be recommended for a renewed comparative study. *Semmer* (1895) reported that tubercle as well as glanders bacilli produce big inflations filled with bright granules, like those to be found within the rods, which are able to reproduce rods and threads after being liberated. *Stoklasa* (1898) saw *B. Ellenbachensis* form "Blasen" and "Kugeln" with numerous motile granules, and *Růžička* (1908) obtained analogous results with *B. anthracis;* here the large globules were seen to liberate their granular content, which was interspersed with very small rods. In view of all these facts it is not easy to understand how *Fuhrmann* (1906–1913) could reach the standpoint and adhere to it that the process observed by him, viz., the formation of large pear-shaped cells or clubs containing and liberating either small motile granules or young rods, i. e., the development of typical gonidangia, be restricted to that group of bacteria which he happened to study (some Pseudomonas species), while it is, in fact, quite general with all bacteria.

The many inflations observed by *Hollandt* (1906) within thick threads of Actinomyces revealed their true character by the regular manner in which their content divided itself into 4 and 16 parts (gonidia). The resemblance to what *F. Cohn* called a "sporangium" of Crenothrix, reproduced as figure 43 on Plate L, is obvious.

On the other hand, *Herzog* (1910–1913), *Lehmann* and *Neumann* (1912), and others have noticed that the so-called giant forms of micrococci, especially those of gono- and meningococci, produce small granules, which the first author found able to reproduce normal cells. The similarity to the gonidangia of the streptococci, mentioned above, is again very clear. And if all these important facts would not have been so utterly neglected by the textbooks *Hort* (1917 *b*) certainly would not have been inclined to remove the meningococcus to the Hemiascomycetes, because once more he observed the upgrowth of normal cells to "giant forms," producing small granules, which in their turn became again normal cocci. A photo-

graph published in our first preliminary report (*Löhnis* and *Smith*, 1916 *a*, original fig. 5), illustrating the liberation of the gonidia from gonidangia of Azotobacter has been reproduced as figure 191 on Plate XV. With *B. fusiformis Rosenow* and *Tunnicliff* (1912) saw small "cocci" escape from the swollen ends of the threads. *Almquist* (1916) obtained small globules, as well as straight and curved rods, from the gonidangia of *B. typhi*. That the characteristic "involution forms" of *B. pestis* are also gonidangia is clearly indicated by the drawings made by *Albrecht* and *Ghon* (1900), which were reproduced as figure 11 on Plate D. The same holds true concerning the inflated big threads of *B. coli*, photographed by *Matzuschita* (1900) and reproduced as figure 36 on Plate III; and it is not to be doubted that many other so-called involution forms, especially most of the globular, pear-shaped, clubbed or otherwise inflated cells, so common within all groups of the bacteria, will find a similar explanation, as soon as adequate attention will be granted to them.

The form of the gonidia is usually, but not always, exactly spherical. Sometimes they are more or less ovoid, or even rectangular or square, as a result of the limited space wherein they are often compelled to grow. Their staining reaction changes necessarily according to their varying chemical composition. (See pp. 112–113.) Sometimes they refuse entirely to be stained by aqueous dyes, as was recorded, for instance, by *Esmarch* (1887) with *Spirillum rubrum*, by *Kedzior* (1896) with *Actinomyces thermophilus*, by *Kuntze* (1904) with *B. oxalaticus*, by *Růžička* (1908) with *B. anthracis*, by *Mencl* (1911) with Azotobacter, and by *Balfour* (1911 *a*) with spirochaets. But more often they stain as well as or even better than the parent cells. Thus were the results obtained, for instance, by *Finkler* and *Prior* (1884–1885) with *V. proteus* and *cholerae*, by *Bostroem* (1890) with *Actinomyces hominis*, by *Stoklasa* (1898) with *B. Ellenbachensis*, by *Thiercelin* and *Jouhaud* (1903) with Enterococcus, by *Tunnicliff* (1906) with *B. fusiformis*, and by *D. H. Jones* (1913) with Azotobacter. When treated with Gram's method, the gonidia are often stained, even if the cells themselves are Gram-negative. *B. radicicola* and its relatives are prominent examples in this direction (*Löhnis*, 1905 *a*). Occasionally special staining methods may give good results, as were secured e. g. by *A. Neisser* (1888) with *B. xerosis*, and by *Bliesener* (1901) with *V. cholerae*, while the gonidia of *Esmarch's Spirillum rubrum*, on the other hand, could not be stained by any of these methods. The metachromatic reaction of the gonidia to methylen blue seems to be fairly constant, according to *Babes* (1895, 1907 *a*, 1914) and *Fuhrmann* (1906–1908). The Romanowsky method gave *Balfour* (1911 *a*) only negative results with the "infective granules" of spirochaets. *Herzog* (1910), on the other hand, noticed that the gonidia of gono- and meningococci turned red when treated with Giemsa's modification of the Romanowsky stain; but when growing up to the full size of the parent cell they assumed more and more the normal deep violet color.

Active motility seems to be more frequent among the gonidia than among their parent cells. *Geddes* and *Ewart* (1878), *Künstler* (1885), and *Dowdeswell* recorded this fact with gonidia produced by spirilla. *Heydenreich*, *Guttmann* (1880), and *Albrecht* (1881) were the first to report the same occurrence with spirochaets. *Beijerinck* (1888), *Frank* (1890), *Atkinson* (1893), *Greig-Smith* (1900), and many others have studied the "swarming bodies" or "zoospores" of *B. radicicola*. Motile gonidia of Actinomycetes were observed by *Eppinger* (1890), *Rullmann* (1896) and *Kedzior* (1896), of *B. anthracis* by *Podwyssotzky* and *Taranoukhine* (1898), of *B. oxalaticus* by *Kuntze* (1904), of *B. subtilis* by *Marrassini* (1913), and of Azotobacter by *D. H. Jones* (1913). Photographs made by the two last-named authors were reproduced as figures 160 and 161 on Plate XII. It is hardly necessary to emphasize, that the minute size of the gonidia makes it especially imperative to distinguish sharply between active motility and Brownian movement. Comparative tests without and with antiseptics are often advisable.

The development of the gonidia may start either inside or outside of the parent cell. If the gonidia are not liberated by the partial or complete dissolution of the cell wall, but remain confined within the cell, they develop into either buds or branches. The great multitude of forms which results from such development, may be seen from the pictures of *B. coli* and *typhi*, made by *Hort* (1917 *a*) and reproduced as figures 179 and 180 on Plate XIII. *Zopf* (1879) was apparently the first to notice this formation of branches in the case of Crenothrix. *Migula*

(1900) has later assumed that the gonidia do not germinate inside, but outside, of the cell wall, to which they were said to be sticking; and he illustrated his theory by the drawings reproduced as figure 69 on Plate P (from original fig. 43 *f* and *g*). However, observations made by *Rullmann* (1907) and by *Ellis* (1907–1910) have confirmed *Zopf's* findings, not *Migula's* assumption. *Hollandt* (1906) got analogous results with the large Crenothrix-like threads of Actinomyces, which he discovered. *Spirillum endoparagogicum*, as described by *Sorokin* (1887), is the only example of this kind of bacterial development which has been frequently quoted in the textbooks. A glance at his drawings, reproduced as figure 29 on Plate H, will suffice to show that, in fact, it was by no means such an exceptional occurrence as it has been usually considered to be. *Kutscher* (1895) recorded similar findings with *Spirillum Undula*, and *Meirowsky* (1914 *b*) has proved the general occurrence of such branching. His drawings, reproduced as figure 30 on Plate H and on Plate XIV, make interesting counterparts to *Sorokin's* sketches. The lateral germination of the gonidia in *B. xerosis*, as studied by *A. Neisser* (1888), has been another early and exceptionally clear observation of the same principle. *Eppinger* (1890), too, followed carefully the gradual development of the gonidia, appearing within the threads of his *Cladothrix* (i. e. *Actinomyces*) *asteroides*, first into buds, and later into branches. In regard to the typhoid bacillus *Almquist* (1893) was the first to point out that its multiplication is not only caused by fission, but also by producing new rods by budding and branching. His later publications (*Almquist*, 1904–1918) confirmed and extended these findings, now also with respect to *V. cholerae*, *B. dysenteriae* and *paratyphosus*. The sprouting of very thin, needle-like rods, to which the Swedish author paid special attention, is also well noticeable in *Hort's* drawings of *B. typhosus* on Plate XIII (fig. 179).

The results recorded by *Escherich* (1894, p. 87) with *B. diphtheriae* are practically duplicating those of *A. Neisser* with *B. xerosis*, and the description given by *Fraenkel* (1895) of the formation of branches by the diphtheria bacillus is in complete agreement with that given by *Eppinger* for *Actinomyces asteroides*. *Hill* (1902) has pointed out that not always a granule is visible at the base of a branch in *B. diphtheriae* and that its presence, therefore, is not closely connected with the formation of the branch. This point needs further study. It may be that the bacteria are also able to produce branches in the same manner as the fungi do, but this fact, of course, would not interfere with the special rôle played by the growing gonidia in the life of the bacterial cell.

A close relation between the "metachromatic granules" and the formation of buds and branches by various bacteria has been emphasized by *Babes* (1895). *Kedzior* (1896), too, noticed how bright granules contained within the threads of his thermophilic actinomyces extruded into buds and branches. The observations made by *Stolz* (1897) with a diphtheroid organism, by *Craig* (1898), *Cornet* and *Meyer* (1903, p. 83) and by *Fontes* (1910) with *B. tuberculosis*, by *Conradi* (1900) with the glanders bacillus, by *Neukirch* (1902) and by *E. Levy* (1902) with Actinomycetes, by *Greig-Smith* (1900), *Faber* (1912) and *Georgevitch* with *B. radicicola* and *Mycobact. Rubiacearum*, and by *Bajardi* (1903) with *V. lingualis*, all confirm this relation. Most of these authors report that the chromatin granule, which *Georgevitch* called "le centre cinétique," slips into the young branch, where it is to be found at its apex.

A photograph made by *E. de Negri* (1916, original fig. 27), showing excellent budding of her Corynebacterium causing malignous granulom, has been reproduced as figure 184 on Plate XV. Another one of *B. coli*, made by *Kellerman* and *Scales* (1916) is to be seen in figure 185 on Plate XV. The next two pictures (figs. 186 and 187) are reproductions from our first paper (*Löhnis* and *Smith*, 1916 *a*, original figs. 3 and 4); both present budding Azotobacter cells, the last one furnishing an especially clear insight into the relation existing between branches and gonidia retained within the parent cell.

The development of the gonidia within or while still united with the parent cell may also lead to some other modes of development. Figure 188, reproduced from our second preliminary report (1916 *b*, original fig. 1) illustrates a case where the budding gonidia grew up to full sized cells, which now give the parent cell a queer, turtle-like appearance. More frequent, however, although rare compared with the common budding and branching, is the development of full-sized cells from the gonidia while still confined within the parent cell. Naturally, only large

cells like Azotobacter offer sufficient space for such direct internal upgrowth. Figures 190 and 193 on Plate XV, reproduced from our first paper (1916 *a*, original figs. 6 and 21) may illustrate this possibility. *Prażmowski's* (1912) report on Azotobacter contains some similar drawings. The giant Bacterioidomonas, discovered by *Künstler* (1884), which was later described anew as Metabacterium by *Chatton* and *Pérard* (1913), whose drawings were reproduced as figure 50 on Plate M, furnishes an interesting counterpart. With the smaller bacteria such kind of upgrowth is only possible, of course, after the parent cells have enlarged themselves to gonidangia, becoming the "Bakteriensäckchen" of *Schroen* (1890) or the "Ammen" of *Finkler* and *Prior* (1884). The sketches made by *Tomaschek* (1888) and by *Babes* (1895), which were reproduced as figures 51 and 53, Plate N, should be compared in this respect. The large cells of the protean air bacillus studied by *Matzuschita* (1902) furnish another example in this direction. (See fig. 5 on Plate B.)

If the gonidia are liberated as such, their further development, quite naturally, is subject to many more uncertainties. They may become free by a complete dissolution of the cell wall or they may emerge at one point as a "cloud" or as a string of granules embedded in a small or large quantity of other plasmatic material. What *Meirowsky* (1914 *b*) called "umbels" (Dolden) have been evidently in some cases such masses of liberated gonidia, while in other cases it seems more probable that flakes of symplasm have been present, as may be seen from his drawings reproduced on Plate XIII (fig. 178) and on Plate XIV.

A sufficient supply of nutrient material furnished by the parent cell undoubtedly assures and facilitates the new development considerably. The starlike arrangement occasionally noticeable with all bacteria may be caused by the outgrowth of young rods from such liberated cell content, as was illustrated already by one of our Azotobacter photographs, reproduced as figure 176 on Plate XII. *Hort's* pictures on Plate XIII (figs. 179 and 180) contain some similar stars, produced by *B. typhosus* and *B. coli*. They have been frequently observed with *B. radicicola* and *radiobacter* by *Beijerinck* (1888), *Beijerinck* and *Delden* (1902), and myself (*Löhnis*, 1905 *a*). Not all stars, however, are the result of this kind of development. In Chapter III a radiate outgrowth from the symplasm will have to be mentioned, and in Chapter IV a similar grouping of full-grown bacteria in the conjunct stage.

If the amount of nutrient material supplied by the parent cell is insufficient, or if it is quickly dispersed by dissolution, the development of the liberated gonidia depends preeminently on the substrate which they will find. *Lagerheim* (1900) observed that the gonidia of his *Sarcinastrum Urosporae* increased in size and germinated to new rods only if they had a chance to settle down on their natural substrate, viz., a thread of Urospora. When discussing the behavior of the filterable gonidia more examples will have to be mentioned which furnish some valuable information concerning the important effect which the substrate exerts in such cases. In artificial cultures often no upgrowth was noticeable on account of unsuitable environmental conditions; not a few failures, however, have been caused, as may be safely assumed, by the widespread inclination to consider "granular decomposition" and "autolysis" of the bacteria as full proof of their death and therefore justifying the discarding of all such cultures. That this custom does not take into account the important rôle played by the symplasm in the life history of the bacteria will be proved by the facts to be discussed in Chapter III. At present it may suffice to refer only to the observations made by *Fuhrmann* (1906) with regard to the behavior of the metachromatic granules (i. e. gonidia), imbedded in the "detritus," which results from the disintegration of the club-shaped gonidangia of *Pseudomonas cerevisiae* and related forms. He reports that at the end of the life cycle there were present only—

die stärker lichtbrechenden, mit Methylenazur rot-violett färbbaren Kügelchen, aus denen sich wieder bewegliche Kurzstäbchen rückbilden, sobald der Detritus auf einen neuen Nährboden übertragen wird.

If the conditions are not favorable to an immediate upgrowth of normal cells, the gonidia may multiply as such for a considerable length of time, either by fission or by budding. This mode of development was reported in 1865 by *Hallier* for the so-called *Leptothrix buccalis*. In 1878 *Geddes* and *Ewart* studied the same process with some water spirilla, and at the same

time *J. Israël* with Actinomyces. *Zopf* (1879–95) saw the gonidia of Crenothrix and of Beggiatoa behave in the same manner. Analogous results were recorded with *B. anthracis* by *Archangelski* (1883), with *B. Chauvoei* by *Ehlers* (1884), with *B. allantoides* by *L. Klein* (1889), with *B. coli* by *Almquist* (1893), by *Adami, Abbott* and *Nicholson* (1899) and by *M. E. Abbott* (1900), with *B. typhosus, paratyphosus, dysenteriae,* and *pseudodysenteriae* by *Almquist* (1893–1908), with *V. cholerae* by *Cunningham* (1897), by *Almquist* (1904–8), and by *Stamm* (1914), with various spirochaets by *Wechselmann* and *Löwenthal* (1905), *Henry* (1913) and others, with *B. tuberculosis* by *Fontes* (1910), and by *Maher* (1910–1915), with Azotobacter by *Prażmowski* (1912). Macroscopically this kind of development is usually very inconspicuous; on solid substrates nothing more will be seen than a very thin dewy layer without any pigmentation, while in liquids either a weak turbidity or a fine cloud of sediment becomes noticeable. Nevertheless, the pathogenicity may be fully retained as was discovered by *Archangelski* in 1883.

In those cases where the environmental conditions allow an upgrowth of the liberated gonidia, they may, as it is also very often done by the gonidia budding out from the parent cell, first develop to regenerative bodies before reproducing normal vegetative cells. This possibility will be discussed later. The direct germination of a new vegetative cell from a gonidium has been first recorded by *Perty* (1852). *Hallier* (1865) and *Karsten* (1869) probably observed the same process, which then was firmly established by *F. Cohn* (1870) by his investigations upon the germination of the gonidia of Crenothrix. *Rindfleisch* (1872) made some interesting drawings of germinating gonidia, which were reproduced as figure 41 on Plate K. *Zopf* (1879) confirmed *Cohn's* findings, but he also pointed out that by no means all gonidia can be expected to germinate promptly when placed under the microscope. In his important investigations upon the gonidangia formation of *B. anthracis, Toussaint* (1884) also studied the upgrowth of new rods from the liberated gonidia. The same has been done with *V. cholerae* by *Dowdeswell* (1889), *Bliesener* (1901), *Fedorowitsch* (1902) and *Almquist* (1904), with *V. proteus* by *Finkler* and *Prior* (1884–1885), and by *Firtsch* (1888), with other spirilla by *Künstler* (1885), with *Actinomyces hominis* by *Bostroem* (1890), with *B. coli* and *typhosus* by *Almquist* (1893) and by *Fedorowitsch* (1902), the latter in addition recorded analogous results with *B. pyocyaneus, cholerae gallinarum, septicaemiae murium, diphtheriae,* and *tuberculosis,* with *B. diptheriae* also by *Cache* (1901), with *B. tuberculosis* by *Arloing* (1908), with *B. mallei* by *Marx* (1899), with Enterococcus by *Thiercelin* and *Jouhaud* (1903), with *B. fusiformis* by *Tunnicliff* (1906) with *Spirochaeta gallinarum* by *Hindle* (1911), and with Azotobacter by *Prażmowski* (1912). Practically this germination consists merely in an expansion and stretching of the small gonidium to the normal size of the vegetative cell, as it was pictured, for instance, by *N. K. Schultz* (1901 *a*) with *B. pestis.* (See fig. 58 on Pl. O.) Sometimes the original membrane may be left behind, which fact naturally is more easily discovered with the large trichobacteria than with smaller species. Drawings made by *Billet* (1890) of germinating *Cladothrix* gonidia, reproduced as figure 70 on Plate P (from original figs. 4 and 5 on Pl. IV) may serve as an illustration. *Woloschin* (1913) once observed that under certain conditions the capsules of *B. anthracis* break up, and that then from these apparently empty broken sheaths new bacilli may germinate, a fact which induced him to formulate the somewhat vague hypothesis, that the substance of the capsules itself be endowed with an "embryonic life". Undoubtedly, it is much more probable that those unstainable gonidia, especially frequent with spore-forming bacilli, after budding out from the parent cell have remained within the equally unstainable capsule, thus apparently becoming a part of it.

That the resistance of the gonidia is not much higher than that of the vegetative cell has been pointed out before. They are organs for multiplication and reproduction and do not possess any special protection against deleterious influences, except that given by the higher concentration of their plasmatic body and by the resulting reduction in moisture content. Naturally they can not withstand boiling water, but it has been frequently noticed that other noxious influences active in nature which destroy the life of the vegetative cell can be endured by the gonidia, which, therefore, also in this respect may occasionally play an important rôle. *Finkler* and *Prior* (1885), for instance, ascertained that the gonidia of their vibrio proved to be

only a little more resistant at 65° C., but much more so against sharp drying at room temperature (above P_2O_5); and in old cultures they retained their reproductive power for months. According to *Esmarch* (1887) dried cultures of his *Spirillum rubrum*, which had not yet produced their gonidia, died within 6–8 days, while the vitality under the same conditions was fully retained for more than five weeks, when the gonidia were formed, though these also in this case were killed in water of 52° C. within five minutes. *Bliesener* (1901), too, found that the gonidia of *V. cholerae* were killed if exposed to 50° C. for 30 minutes. Sharp drying also proved to be detrimental; but in water the vitality was retained for nearly three years, and the author, therefore, thinks that under natural conditions they may occasionally conserve the life for a considerable length of time. The results obtained by *N. K. Schultz* (1901) with *B. pestis*, and by *Rothert* (1902), as well as by *Fedorowitsch* (1902) and by *Martini* (1910) with several other non-spore-forming bacilli (*Staphyloc. pyogenes*, *Streptoc. pyogenes*, *B. coli*, *typhosus*, *dysenteriae pneumoniae*, *pyocyaneus*, *septicaemiae*, and others) were quite similar. Old sealed cultures of the plague bacillus were found by *Schultz* to be still alive after four years, and *Fedorowitsch* reported that a culture of *B. pyocyaneus* died within 3–8 days, if it was dried when only 5–6 hours old, but that it lived for 38 days when it was allowed to grow 24 hours, so as to form gonidia before being dried. With *Bac. cholerae gallinarum* the following data were recorded:

Age of culture before drying	4–8 hours.	24 hours.	5 days.
Limit of vitality was reached after	22–25 days.	97 days.	84 days.

B. coli was completely killed, according to *Schultz* and *Ritz* (1910), if a 3–6 hours culture was kept for 25 minutes at 53° C., while 12–24 hour cultures gave about the same number of colonies on the plates made from the not heated and from the heated suspensions.

The very considerable resistance of diphtheria and tubercle bacilli against drying, which *Chester* (1901) connects with the presence of "gonidia", is evidently due to their having changed into the more resistant regenerative bodies, though a somewhat greater resistance of the genuine gonidia in this case is also quite probable. *Jessen* and *Rabinowitsch* (1910)reported that the small acid-fast granules of tubercle bacilli remain intact, when the bacilli themselves are solved by caustic alkali. The so-called granular decomposition of cholera and of other organisms in the serum is undoubtedly, partially at least, another indication of the increased resistance of the gonidia. And the same holds true with regard to the fact that slightly detrimental influences, which reduce the vitality of the vegetative cells, stimulate the formation of the gonidia, a fact which has been studied by *Ruata* (1905) with *V. cholerae*, which was treated with free ammonia. *Balfour* (1911 *a*) has emphasized the greater resistance of the gonidia of spirochaets against salvarsan, and the resulting difficulty in curing chronic spirochaetosis. This point deserves to be studied, mutatis mutandis, in other chronic diseases, too.

(2) REGENERATIVE BODIES AND EXOSPORES.

According to the definition given on page 121 the so-called regenerative bodies are produced either by the gonidia or by the symplasm. It would be preferable if only the first category of them could be considered here and the others be left to Chapter III. But the data available at present often do not allow such a sharp distinction, and therefore the subject must be treated in a somewhat loose manner. Details relating to the transformation of the symplasm into regenerative bodies will be discussed in Chapter III; the appearance and behavior of the fully developed regenerative bodies, however, will be better considered here, as it is often not only difficult, but even impossible to decide exactly whether observations recorded in the literature refer to regenerative bodies developed from the gonidial or from the symplastic stage.

The first type of formation of regenerative bodies, consisting in the upgrowth of gonidia to bodies of larger size and of more solid structure, is very common among the bacteria and has been noticed, therefore, by many investigators. Especially the development of the large deeply staining globular regenerative bodies at the side or at the end of the normal bacteria, has often evoked more or less interest. The photographs reproduced as figures 116, 124, 126–129 on Plate X, nearly all on Plate XI, figures 170–172 on Plate XII, those on Plate XIII, and the drawings made by *Henneberg* (1898), which were reproduced as figure 57 on Plate N,

will convey some idea of their general occurrence. In addition, a few drawings made by *Niessen* (1898) from his so-called syphilis bacillus have been reproduced as figure 194 on Plate XV, because they demonstrate especially well the characteristic appearance of this type of reproductive organs. The following description, given by *Fuhrmann* (1906) also deserves to be quoted; after having discussed the rôle played by the "clubs" (i. e. gonidangia) in the life history of *Pseudomonas cerevisiae* and related species he continues:

> Es sind noch eigentümliche Bildungen zu nennen, die dann auftreten, wenn die verlängerten Stäbchen in optimale Lebensbedingungen gebracht werden. Es bilden sich dann am Stäbchen kleine Wärzchen, die sich vergrössern und endlich ablösen und frei in der Flüssigkeit schweben. Bei manchen von ihnen kann man nun eine Aufteilung des Inhaltes beobachten. Die Teilstücke werden dann frei und gleichen allerkleinsten Stäbchen und Pünktchen.

When the formation of the regenerative body takes place at the end of the cell, the resulting picture resembles very much that of a plectridium, but the regular bright spore is replaced by the deeply staining regenerative body. The drawings reproduced as figure 71 on Plate P may illustrate this possibility. They were taken from a paper upon *Spirochaeta icterohaemorrhagica*, published by *Inada, Ido, Hoki, Kaneko and Ito* (1916, original figs. 40–47 on Pl. 61).

With micro- and streptococci it is often difficult to discern exactly whether the body formed should be classed as regenerative body or as microcyst. Our photographs of *Microc. candicans*, reproduced as figure 168 on Plate XII, and the drawings made by *Babes* (1895) of branching streptococci, reproduced as figure 3 on Plate B, may serve as examples in this direction. On the other hand, our photograph of *Streptoc lactis*, reproduced as figure 170 on Plate XII, demonstrates equally well the budding out of the gonidium and its upgrowth to a lateral regenerative body. A picture of *Streptoc. pyogenes* published by *Hewlett* (1902) and reproduced as figure 72 on Plate P (from original fig. II*a*) shows the same details, as does also the first sketch of those made by *Hlava* (1902) of his *Leuconostoc hominis*, which have been reproduced as figure 4 on Plate B.

Among the nonspore-forming short rods very instructive preparates are easily obtainable especially with *B. radicicola* and with the lactobacilli (*B. acidophilus*, *casei*, etc.). Two characteristic photographs of *B. radicicola* made by *Hiltner* and *Störmer* (1903, original figs. II, 1 and 2) are reproduced as figures 195 and 196 on Plate XV. *Bac. bulgaricus* has been shown in figures 148 on Plate XI and 172 on Plate XII; other pictures of closely related organisms may be found in papers of *Weigmann, Gruber* and *Huss* (1907), *Kuntze* (1908), and *White* and *Avery* (1909). The picture made by *Tissier* (1900) of *B. bifidus*, reproduced as figure 8 on Plate C, is also of interest in this connection. Some of the photographs by *Almquist* (1916–1917), showing regenerative bodies of *B. typhosus, dysenteriae* and of other nonspore-forming bacteria, were reproduced as figures 135–138 on Plate XI.

The branched threads of *B. subtilis* reproduced as figure 197 on Plate XV from our second preliminary paper (*Löhnis* and *Smith*, 1916 *b*, fig. 27) exhibit at the same time small, pale, budding gonidia, well developed regenerative bodies in lateral, as well as in terminal, position, and also an unstainable body, apparently a growing exospore. Interesting details concerning the formation of regenerative bodies by the gonidia of Azotobacter have been published by *Prazmowski* (1912, pp. 145–147), who paid special attention to their development from the liberated gonidia. The so-called micro-oidia, described by *Bredemann* (1909) for *B. Amylobacter* and by *Viehoever* (1913) for *B. Pasteurii*, are probably also to be classed as regenerative bodies, though they have not been seen to reproduce normal rods. Similar round forms have been observed by *E. Klein* (1883) with *B. anthracis*, but here their formation, as well as their ability to reproduce normal rods, have been carefully studied and ascertained.

With spirilla and vibrios lateral, as well as terminal, regenerative bodies are equally frequent. The so-called arthospores of *V. cholerae* found by *Hueppe* (1885), whose drawings have been reproduced as figure 49 on Plate M, as well as those described by *Firtsch* (1888) for *V. proteus*, have been either regenerative bodies or exospores. The deeply staining resistant organs described by *Weibel* (1888) for his *V. lingualis* are also to be classed as regenerative bodies.

With spirochaets these lateral or terminal swellings are still more conspicuous, and they have been noticed accordingly by practically all authors, who have made such studies. *Künstler* (1885) probably has been the first to mention this occurrence, when he described his "Proteromonas Regnardi." The spirilliform organism isolated by *Calmette* (1893) from typhus cases, whose "spores" were found either to multiply as such (by budding) or to reproduce new "spirilla," apparently also belongs in this group. More recent and more complete, though often misinterpreted, evidence relating to spirochaets has been furnished by *Prowazek* (1906), *Mühlens* and *Hartmann* (1906), *Schaudinn* (1907), *Fantham* (1911), *Hindle* (1911), *Noguchi* (1911–1912), *Wolbach* (1914), *Meirowsky* (1914), *Inada, Ido, Hoki, Kaneko* and *Ito* (1916), as well as by *Leishman* (1918). *Noguchi* (1912) has pointed out with good reason, that these formations "should not be viewed as the result of plasmoptysis" because "the number of the organisms with round bodies . . . seems to become greater where the growth of the culture approaches its maximum" and the development of new spirochaets from these bodies also has been observed. Some very interesting pictures made by *Inada* et al. (1916) have been reproduced as figure 31 on Plate H; they make a good counterpart to our Subtilis photograph (fig. 197 on Plate XV).

That fusiform bacilli behave in the same manner as spirochaets do, was noticed by *Ellermann* (1907), but he discarded the round bodies once more as "involution forms."

Most frequently their presence has been recorded with the Mycobacteriaceae. The fairly resistant, but easily stainable round reproductive organs formed usually at the ends, but also at the sides of *B. tuberculosis, leprae, mallei, diphtheriae*, and *pseudo-diphtheriae* have attracted considerable attention. The earliest observations in this direction have been those of *A. Neisser* (1881) and *G. A. Hansen* (1882) upon the formation of globular "spores" of *B. leprae*. They were confirmed by *Babes* (1883), who in addition discovered the analogous organs of *B. tuberculosis*, and more completely by *Lutz* (1886). Similar results were later recorded for *B. leprae* by *Bordoni-Uffreduzzi* (1888*a*), *Czaplewski* (1898) and by *Meirowsky* (1914*b*), for *B. mallei* by *Semmer* (1895), *Galli-Valerio* (1900) and by *Carpano* (1913), for diphtheroid organisms by *Nakanishi* (1900*c*) and by *E. de Negri* (1916), for *B. diphtheriae* by *Bergstrand* (1918), for *B. tuberculosis* by *Sander* (1893), *Semmer* (1895), *Crookshank* (1896), *Droba* (1901), *W. Ernst* (1902), *Meier* (1903), *Schroen* (1904), *Rosenblat* (1905), *Betegh* (1908), *Meirowsky* (1914*b*), and by others.

The deeply staining "spores" seen by *Schütze* (1908) to grow singly at the end of the branches of *Actinomyces monosporus* evidently have also been regenerative bodies, and the same seems to hold true with regard to the spherical spore-like body found by *Metchnikoff* (1888*b*) to be produced within the club-shaped cells of his *Pasteuria ramosa*.

The form of the terminal regenerative bodies is either globular, oval, or pear-shaped, while those in lateral position are either spherical or kidney-shaped. After being liberated, they all seem to assume a perfectly spherical form. Whether the regenerative bodies of irregular shape, frequently to be seen in the cultures, are exclusively produced by the symplasm or by normal vegetative cells, also, can not be decided at present. The first-named possibility, however, seems to be more probable.

All regenerative bodies take the stain very readily, so that under the microscope, as well as in the photographs, these comparatively large dark bodies are very conspicuous.

Motility seems to be absent as a rule. In those cases, where motile gonidia grow up to regenerative bodies after being liberated, these too, may retain motility for some time, though it is, of course, under such conditions a more or less disputable point, at what moment the "gonidium" actually becomes a "regenerative body." Especially with *V. cholerae* repeatedly large globular bodies have been observed, e. g. by *Dowdeswell* (1889), *Hammerl* (1906), *Almquist* (1908) and *Bittrolff* (1912), which, indeed, may have been motile regenerative bodies. *Almquist* (1907) reports, that also in the case of *B. typhi* he saw motile globules separate themselves from the bacilli, which being able to germinate promptly apparently have been genuine regenerative bodies.

Further development from the regenerative bodies is naturally more easily to be ascertained than it is usually the case with the gonidia. But here again occasionally fragmentation and dissolution may be seen, which processes should not be taken by themselves as proof of "involution" and death. Generally the irregularly shaped regenerative bodies seem not to be able to reproduce directly normal vegetative cells. One often sees them either breaking up into round regenerative bodies, which germinate later, or melting together to a flake of symplasm, which in its turn may produce either directly normal vegetative cells or another set of regenerative bodies of regular shape. Such fragmentation and dissolution have been repeatedly reported, for instance with so-called bacteroids of the root-nodule bacteria by *Beijerinck* (1888), *Moeller* (1890), *Hiltner* and *Störmer* (1903) and others. The irregular regenerative bodies of spore-forming bacilli, as well as those of micrococci, behave in the same manner, as was discussed in our preliminary papers (*Löhnis* and *Smith*, 1916 *a* and *b*). That *Buchanan* and others have seen the "bacteroids" of *B. radicicola* proliferate as such or produce small motile rods by segmentation, should not be considered to be irreconcilable with the facts just mentioned. "Bacteroids" behaving in this manner are merely branched vegetative cells, which may be morphologically more or less similar to those other forms, though they are different physiologically.

The globular regenerative bodies are much inclined to multiply as such, before reproducing normal vegetative cells. Like the gonidia, they multiply by budding as well as by fission; both processes may be often seen to proceed side by side in the same preparation. The resulting "pure cultures" of budding, relatively large, coccoid cells may look very similar, though actually belonging to entirely different organisms. *Eyre* and *Washburn* (1897) obtained such a luxuriantly growing, avirulent, gelatin liquefying culture of resistant micrococci from a typical pathogenic Pneumococcus. Numerous photographs, reproduced on our plates, illustrate the analogous behavior of various species as observed by different authors. These are:

II, 18: *Bact. bruneum* (*fluorescens* var.), *Matzuschita* (1900).
III, 30: *Bact. cholerae gallinarum*, *Itzerott* and *Niemann* (1895).
III, 35: *Bact. pestis*, *Rowland*, (1912).
V, 59: *Bac. anthracis*. *Henri* (1914).
VI, 68: *Bac. Azotobacter*, *Löhnis* and *Hanzawa* (1914).
VIII, 91: *Bac. mallei*, *Carpano* (1913).
IX, 97: *Bac. diphtheriae*, *J. Dale* (1910).
IX, 98: *Bac. variabilis lymphae vaccinalis*, *Nakanishi* (1900c).
IX, 101: *Corynebacterium of malignous granulom*, *E. de Negri* (1916).
IX, 104: *Bac. tuberculosis*, *Arrigo* (1900).
XI, 146: *Streptococcus lanceolatus*, *Axelrad* (1903).
XI, 147: *Bact. coli*, *Axelrad* (1903).
XII, 154: *Bac. leprae*, *Kedrowski* (1910).
XII, 155 and 156: *Meningitis bacillus*, *Ghon*, *Mucha* and *Müller* (1906).
XII, 157: *Bact. cyanogenes*, *Neelsen* (1880).
XII, 158: *Vibrio cholerae*, *Hammerl* (1906).

That the presence of these globular regenerative bodies in practically pure growth within the organism may sometimes cause serious diagnostic errors, has been already mentioned with regard to diphtheria on pages 79 and 80. The general occurrence of such deceptive forms within all groups of bacteria is certainly of considerable importance, and a careful study of their morphological and physiological behavior is much to be recommended. In this connection an observation made by *Calmette* (1893) in regard to a spirilliform organism, isolated from typhus cases, is of interest. The round regenerative bodies grew constantly as such, multiplying by budding, when they were kept on an acid substrate, while an alkaline reaction and substrates rich in albumines stimulated their germination and the regeneration of spiral forms.

It seems not unlikely that several descriptions of so-called cocci actually refer to regenerative bodies of other species. If these "cocci" later changed to rods, or if in old cultures of bacilli such "cocci" have appeared, the "contamination" theory undoubtedly has been often invoked erroneously. I myself have to plead guilty, that for nearly two years I have rejected as "impure" actually pure cultures of aerobic cellulose destroying bacteria, which had been isolated by *Grant Lochhead* (unpublished investigations 1912–1914), because careful examination

of his preparations invariably revealed the reappearance of "cocci," which, as our later studies (*Löhnis* and *Smith*, 1916*b*) have brought out, are constantly to be found in this as in every other group of bacilli. What perplexing pictures are to be had especially from these aerobic cellulose destroying rods may be seen from figure 265 on Plate XXI, which was reproduced from the last-named paper (orig. fig. 52). It was made from a frequently tested pure culture of *Bact. acidulum*, originally described by *Kellerman*, *McBeth*, *Scales* and *Smith* (1913) as a slender short rod (average dimensions $1.0 \times 0.3\mu$).

Even with regard to the Nitrosococcus of *Winogradsky* it is by no means improbable that this is no coccus at all, but a pure culture of regenerative bodies of Nitrosomonas. The photograph made by *Winogradsky* (1891), reproduced as figure 198 on Plate XV, shows besides round cells of rather different size, i. e., a peculiarity much more frequent with regenerative bodies than with genuine cocci, some small short rods, which according to *Winogradsky* represent an "impurity;" the photograph is said to have been made from a "vieille culture sur silice, déjà devenue un peu impure." However, in the lower right corner of figure 198 we see a larger rod connected with a round body exactly in the same manner, as it is shown by all bacilli when producing regenerative bodies and in the upper left corner something like a torn, empty membrane is visible, whose presence also fits much better to the theory that regenerative bodies, not genuine cocci, are represented in this picture. Additional evidence will be furnished in Chapter III. A comparison of figures 198 and 195 (Nitrosococcus and regenerative bodies of *B. radicicola*) is also to be recommended.

The multiplication of irregularly shaped rod-like regenerative bodies is sometimes to be observed with micrococci, and occasionally it becomes so firmly established, that the cultures present a picture much more resembling an Actinomyces than a Micrococcus. Figures 2–6 and 8 on Plate I illustrate this possibility. It is readily to be admitted, of course, that our present knowledge often leaves us in doubt, whether such forms should be classed as regenerative bodies or as truly vegetative cells. Their staining reaction, as well as their ability to reproduce regular micrococci, may often serve as a valuable indication, and their development from the symplasm may supply additional evidence. Further investigations, however, are indispensable to learn more upon the vegetative or reproductive character of such forms.

The germination of rod-like forms from round regenerative bodies has been observed quite frequently viz. with *B. cyanogenes* by *Neelsen* (1880), with *B. typhosus* by *Almquist* (1904), with *B. paratyphosus, dysenteriae*, and *pseudodysenteriae* by the same author (*Almquist*, 1908), with *B. coli* by *Kellerman* and *Scales* (1916), with *B. radicicola* by *Spratt* (1912), with *Proteus hominis capsulatus* by *Bordoni-Uffreduzzi* (1888*b*), with *V. cholerae* by *Hueppe* (1885), *Babes* (1889), *Nakanishi* (1901) and by *Almquist* (1904), with various other vibrios by *Firtsch* (1888), *Kohlbrugge* (1900) and by *Nakanishi* (1901), with spirochaets by *Noguchi* (1912 *d*), with diptheroid organism by *Nakanishi* (1900*c*) and by *E. de Negri* (1916), with *B. leprae* by *Czaplewski* (1898) and by *Meirowsky* (1914*b*), with *B. tuberculosis* by *Rosenblat* (1905) and by *Meirowsky* (1914*b*). The pictures made by the last-named author of *B. tuberculosis, leprae*, and *Spirillum rubrum*, which were reproduced as figures 164, 166, and 167 on Plate XII, as well as his drawings shown on Plate XIV in the column "Freie Knospen and Jugendformen," should be compared with some photographs made by *Kellerman* and *Scales* of germinating regenerative bodies of *B. coli*, reproduced as figures 199 and 200 on Plate XV. That two or three sprouts may break forth simultaneously, as demonstrated in the last-named picture, seems to be no rare occurrence. *Almquist* (1906) mentioned this fact in regard to *B. typhi*, and a photograph made by *Stamm* (1914), reproduced as figure 201 on Plate XV, illustrates the same type of growth with *V. cholerae*. The picture is of special interest, because it shows side by side with germinating regenerative bodies others, which evidently are developing to gonidangia.

The higher resistance of the regenerative bodies against heating, drying, and other unfavorable conditions has evidently exerted its influence where it was noticed that cultures of non-spore-forming bacteria sometimes exhibit a quite considerable resistance. Details in this direction have been repeatedly collected, e. g., by *Ficker* (1898), *Rothert* (1902), *P. Eisenberg* (1908), *Lehmann* and *Neumann* (1912), and by *Bernhardt* (1915). Own experiments with *V. cholerae*

furnished the first-named author the following interesting data. Cultures of different age died, when kept in the humid chamber at 37° C, after 1½, or after more than 50 days in the following succession:

	Days.	Days.	Days.	Days.
Age of the cultures	1	2	3	8
Duration of life	1½	3	14	More than 50

Microscopic studies apparently have not been made in this case, though older observations by *Firtsch* (1888) and by *Weibel* (1888) upon the increased resistance of the globular bodies present in old cultures of other vibrios should have suggested such investigations. *Firtsch* had noticed that the vegetative cells of *V. proteus* died when dried more than ¼–½ hour above sulphuric acid, while their "granules" still germinated after having been dried for 12½ hours; and *Weibel* had found that the "spores" of his *V. saprophiles* withstood the influence of moist heat of 53° C. for more than 24 hours. *Cantacuzène* (1898) reported that the round forms of *V. cholerae* were killed only by temperatures higher than 80° C., and *Almquist* (1916) succeeded by heating cholera cultures up to 60° C. in obtaining a strain, which for two years grew constantly in the round form, but still showed regular agglutination.

Gage (1903) noticed that most cells of *B. coli* and *typhosus* were killed by temperatures of 45–55° C., while some, however, withstood heating up to 85° C. Freezing acted in an analogous manner upon cultures of *B. typhosus, campestris,* and others, when tested by *E. F. Smith* and *Swingle* (1905); the authors suppose that "arthrospores" were present in their cultures. Many round and irregular forms were seen by *Preisz* (1904) in the secondary colonies, developing in old cultures of numerous bacteria, which also showed a considerable increase in longevity. *Spratt* (1912) reported that the round regenerative bodies of *B. radicicola* were even not killed by boiling water, and *Rodella* (1908) made use of the higher resistance of the analogous organs of the lactobacilli for isolating them: he inoculated material 4–5 days old into melted agar kept at 80° C. and left it therein for 2–3 minutes before lowering the temperature.

With diptheroid organisms similar results have been recorded by *A. Neisser* (1888), whose *B. xerosis* in 6-days-old cultures withstood 70° C. for 15 minutes, by *E. Klein* (1900), whose *Bacterium diptheroides* died usually within one week, but lived for many weeks in serum, where it regularly produced oval or spherical cells instead of the normal rods. The Corynebacterium studied by *E. de Negri* (1916) was also killed at 60° C. within one hour, when tested in the rod form, while the budding round cells remained alive. The round deeply staining bodies produced by *Streptobacillus pellagrae* resisted 80° C., according to *Tizzoni* and *Angelis* (1913). *B. mallei* showed only low resistance when tested by *Marx* (1899), but *Bondâme*, according to *Lehmann* and *Neumann* (1912, p. 548), found that occasionally a temperature of 70° C. was endured for 6 hours and that of 90° C. for 3 minutes. *Carpano* (1913) considered the round deeply staining "spores" of the glanders bacillus to be the reason of its remaining alive in the cultures for more than a year. *Schütze* (1908) noticed that the regenerative bodies ("spores") of *Actinomyces monosporus* endured the temperature of 75° C. for 40 minutes.

Sometimes the reproductive organs growing at the side or at the end of the bacteria do not show the characteristic appearance of the normal deeply staining regenerative bodies, but assume more the character of the endospores, especially with regard to their resistance against the ordinary staining methods. On account of their external position we call such bodies exospores. Our photographs of *B. subtilis*, reproduced as figure 197 on Plate XV, and of *B. Azotobacter*, figure 69 on Plate VI, may illustrate this occurence. The simultaneous production of endo- and exospores in the latter case is of special interest. On the other hand, the replacement of deeply staining regenerative bodies by unstained exospores, as shown with *B. subtilis,* seems to be very frequent with spirilla and vibrios. It is not improbable that the so-called arthrospores of *V. cholerae,* described by *Hueppe* (1885), *Babes* (1889), and others, have been, partially at least, exospores. *Weibel* (1888) observed with his different vibrios side by side stained and unstained round bodies, just as we did recently with some salt-water spirilla (*Löhnis* and *Smith,* 1916 *a*). Of his *Spirobacillus Cienkowskii Metchnikoff* (1889) made the drawing reproduced as figure 73 on Plate P (from original fig. 14 on Pl. 1). *Spirillum monospora,* described by *Dobell* (1908), seems to have exhibited a similar appearance. The spore-forming anaerobic

cellulose destroying bacteria, studied by *Prażmowski* (1880) and by *Omelianski* (1902), are another example to be mentioned here. As they are often curved, the first-named author used the old name Vibrio Rugula for them, but probably they should be better placed in the neighborhood of *B. oedematis maligni.* His drawings, showing the terminal spore formation, have been reproduced as figure 28 on Plate H. *Omelianski's* photographs seem to indicate that also in his preparations some of the terminal bodies took the stain, and apparently some lateral regenerative bodies were present, too. In addition his findings concerning the heat resistance of these spores deserves our attention; they withstood 95°, but died quickly at 100° C. It is true that the terminal spores of *B. tetani* and related anaerobic bacilli are characterized by a similarly low resistance. But it is a disputable point whether it is altogether correct to class them as endospores, as is usually done. In my opinion, they too should be accepted as exospores. Their position, forms, and degree of resistance links them obviously more closely to those exospores mentioned above than to the centrally located, highly resistant endospores, formed by the bacilli of the Subtilis-Mesentericus group.

Exospores are also produced occasionally by many other bacteria. *Lutz* (1886) noticed that *B. leprae* sometimes furnishes such bodies. With *B. tuberculosis* terminal spores were recorded by *F. Fischel* (1893), *Hawthorn* (1903 *b*), and by *Wherry* (1913), with *B. pseudo-diphtheriae* by *Simoni* (1898); in the latter case they survived 80° C for more than 10 minutes. Probably those spores of *B. tuberculosis* and *diphtheriae,* which according to the observations made by *Marpmann* (1893) and by *Babes* (see *Cornil* and *Babes,* 1890, Vol. II, p. 59), respectively, were even not killed by boiling, are also to be classed here.

Furthermore, the following so-called nonspore-forming bacteria have shown themselves to be able, under conditions not yet well known, to assume the faculty to produce fairly resistant exospores (or, as they have been usually called, polar endospores). They are *B. acidi lactici* and *B. cyanogenes* (*Hueppe* (1884), *B. typhi* (*Gaffky,* 1884), *B. coli* (*Piccoli,* 1896), *Bact. lactis acidi* (*Weigmann,* 1899) and *Bact. Zopfii* (*Swellengrebel,* 1904). It has been mentioned on page 95 that some of these observations, especially with regard to typhoid and lactic acid bacilli, have been repeatedly refuted. Nevertheless, they, too, deserve a renewed study. That in all these cases invariably, and in most of them quite independently, polar spores have been found, is certainly not without importance. On the other hand, some spore-forming bacilli have been described, showing polar spores, too, whose general character brings them very close to usually nonspore-forming bacteria. These are: *B. esterificans Maassen* (1899), closely related to *B. coli; B. violarius acetonicus Bréaudat* (1906), evidently a spore-forming strain of *Bact. violaceum;* and an unnamed morphologically tetanus-like bacillus, growing yellow or red (*Morgenthaler,* 1916), just like *Bact. herbicola.* A closer search among the thousands of species descriptions would undoubtedly furnish more such evidence. But it is of much greater interest, that also the so-called denatured butyric acid bacilli, which have lost their ability to produce normal endospores, which, however, by certain methods can be induced to turn again to sporulation, were found by *Grassberger* and *Schattenfroh* (1907) to form round polar spores, like *B. tetani.* On the other hand, an old weakened culture of *B. anthracis* has been studied by *Chauveau* and *Phisalix* (1895), which had lost its faculty to produce endospores, but instead of these formed quite constantly terminal round bodies, which, however, were killed by temperatures above 70° C., and which could be stained by aqueous dyes, i. e., they were normal round regenerative bodies.

My own findings with Azotobacter and various other usually nonspore-forming bacteria are in full agreement with all these observations. It seems as if the production of terminal round regenerative bodies and of exospores is a necessary step which has to be passed when the formation of endospores is to be developed. Some genera (Spirillum, Vibrio) seem to be unable to reach the latter stage, but in regard to the so-called nonspore-forming rods it will be well worth trying whether or not the newly won insight will open experimental possibilities, which so far never have been tried. A few additional remarks upon this problem will be made on the following pages.

(3) ENDOSPORES.

Formation of endospores may occur within the vegetative rods, as well as within gonidangia and regenerative bodies. Thus far only the first possibility has been studied more thoroughly. According to *Zopf* (1883, p. 66) the granules first visible within the cell unite in making up the spore, but *L. Klein* (1889) studied some species which did not show any granulation of the cell plasma preceding the formation of the spore. As *Hueppe* (1891, p. 29) pointed out, either the whole content of the cell or only a part of it may be used up for that purpose. *Bunge* (1895) accepted only a special class of cell granules as the true elements of spore formation; others, like those seen by *P. Ernst,* were declared to be in no way connected with it. That, however, here as in other cases staining reactions are not very conclusive is clearly indicated by some results recorded by *Zettnow* (1899), who saw the spores, when they were treated with Romanowsky's method, turn red or blue or remain unstained, sometimes only showing a blue spot in the center. *Nakanishi* (1900 *a* and *b*) declared that the endospore be nothing else than a changed nucleus, but he soon modified this statement, saying that the nucleus surrounds itself with chromophilic cytoplasm and so becomes a spore. The spore formation of the large *B. Bütschlii* and *sporonema* was accepted by *Schaudinn* (1902–1903) as some primitive sexual process, to which reference will be made in Chapter IV. The granules present in the cell were seen to increase in number and in size before the spores were formed. *Růžička* (1909) defined spore formation as concentration of the chromatin substance of the cell; later, however, he was of the opinion that the chromatin center "vanish" in old spores. With *Bac. anthracis Péneau* (1911) observed that young cells appeared fairly homogeneous with only some small granules present, which after about 12 hours formed one definite nucleus; this in its turn, about 8 hours later, dissolved into a chromidial system, which ultimately, in the 3–4 days old culture, concentrated itself again, now making the spore. *Swellengrebel* (1913) saw that in his *B. deliensis* the chromatin granules arranged themselves first into straight centrally located or into zigzag filaments, which then in part and under assistance of part of the cytoplasm formed the spore, while the "vegetative" plasma and chromatin, thus separated from the "generative" plasma and chromatin, later dissolves with the rest of the cell. The unequal and in most cases unstable distribution of the nuclear material within the bacterial cell, which has been discussed on page 109, makes all these more or less divergent findings concerning spore formation quite comprehensible.

Occurrence of two endospores within one cell has been recorded by *A. Koch* (1888) for *B. inflatus* and *ventriculus*, and by *Vuillemin* (1903) for *Clostridium disporum.* The spore-forming cells in these cases have been all more or less inflated. The last-named author dwells upon this point, reaching the conclusion that spores formed under such conditions should be differentiated from the normal endospores as "cystospores," and the sporulating inflated cell should be called accordingly "sporocyst." That this point of view was fairly correct is proved by the fact that double and multiple spore formation may be shown by regenerative bodies, as well as by those inflated globular, pear- or club-shaped cells, which normally act as gonidangia. As it is fundamentally the same nuclear material, which, in the form of gonidia, regenerative bodies, exo- or endospores, serves the one purpose of reproduction, it is by no means surprising, that one type of reproductive organ may replace or may pass over into another, especially when we keep in mind that all these separations and classifications are much more artificial than natural. The photographs reproduced as figures 57 on Plate V, 65 on Plate VI and 117–121 on Plate X, showing the apparent or real beginning of spore formation within irregular cells (so-called involution forms, i. e. regenerative bodies and gonidangia) of *B. anthracis* (*Matzuschita,* 1900), *B. subtilis* (*Löhnis* and *Smith* 1916 *a*), *B. Chauvoei* (*Fraenkel* and *Pfeiffer,* 1895), *B. pestis* and *lactis aerogenes* (*Maassen,* 1904), *Proteus vulgaris* (*Hauser,* 1885) and of *V. cholerae* (*Maassen,* 1904), deserve to be studied closely, as they are very suggestive for further investigations along these lines.

A. Fischer (1891, 1903, p. 39), as well as *Migula* (1897, Vol. I, p. 166), were of the opinion that the co-called nonspore-forming bacteria would be eventually found to be able to produce endospores, too; to the first-named author this fact was "beyond doubt." His suggestion that

increased salt content of the substrate will be favorable in this direction, seems to be correct, as was discussed on page 99. And, as far as the nonspore-forming rods come into view, it is indeed probable that they can be induced to form regular endospores or to show themselves to be parts of the life cycles of spore-forming bacilli. With micro- and streptococci, spirilla, spirochaets, and mycobacteria, however, the situation seems to be different. In addition to what has been said above (p. 137) concerning the beginning of spore formation by so-called nonspore-forming rods, it may be pointed out that formation of spores has also been recorded with lactobacilli by *C. Sternberg* (1898) and by *Fokker* (1901), with *B. piscicidus,* a member of the Proteus group, by *N. Sieber* (1895), with members of the Coli-Aerogenes group by *Rogers, Clark* and *Davis* (1914), as well as by *Burton* and *Rettger* (1917), and with *B. fluorescens* by *Tanner* (1918). Microscopic and cultural characters showed otherwise little or no alterations in these cases; similarly, the small monotrichous *Bac. leguminiperdus,* described by *Oven* (1906), displayed much more the appearance of a common "Pseudomonas" than that of an endospore-forming rod. The situation becomes more complicated when the establishment of the ability to form endospores is accompanied by profound changes in morphology and cultural behavior of the organism. Yet this is to be expected and perhaps the rule in all those cases, where genuine endospores are developed, not only those polar "exospores", which stand between regenerative bodies and true endospores. When *Noguchi* (1910) transformed experimentally the anaerobic nonspore-forming *B. bifidus* into an aerobic bacillus closely resembling *B. mesentericus fuscus,* the ever-ready "contamination" theory was eliminated by the fact that the process could be reverted at will. Our own observations are in complete agreement with these findings. There are evidently clearly defined subcycles within the life cycles of the bacilli, which are not only characterized by the absence or presence of endospore formation, but by numerous other differences, too, which fact has thus far practically always misled to the assumption that two or more different species had to be separated, because a close study of the link connecting the different subcycles, viz., of the symplasm, has never been recommended before.

The observations made with cultures of otherwise endospore-forming bacilli, which have lost this ability are of special interest in connection with the facts just mentioned. *Grassberger* and *Schattenfroh* (1907) and many other investigators have noticed that anaerobic butyric acid bacilli not infrequently turn over into quite different aerobic nonspore-forming rods, which, like the asporogenous strains of the Anthrax-Subtilis-Mesentericus group, are microscopically, as well as culturally, much more similar to *B. coli* or *aerogenes* or to some lactobacillus than to their own sporulating parent organism. Sometimes they may also exhibit a more or less Actinomyces-like growth, as was obtained, for instance, from *B. anthracis* by *Nadson* and *Adamovič* (1912), as well as by *Henri* (1914). Of course, there is also the possibility merely to suppress the spore formation temporarily without otherwise changing the character of a strain to any considerable extent, as is often easily performed, e. g., by keeping the bacilli in milk; but this case should not be confounded with the real transformation of a strain, which change is always accompanied by more or less fundamental, morphological, as well as physiological, alterations, such as were observed, for instance, by *Winogradsky* (1902), *Passini* (1905), *Grassberger* (1905), and *Grassberger* and *Schattenfroh* (1907).

When the accidental loss of spore formation was studied for the first time by *Lehmann* (1887), it was found that instead of the regular endospores only "micro-spores" were produced, which, however, were killed when kept for 2–3 hours at 60° C. This observation was soon confirmed by *Roux* (1890) and others. More recently *Růžička* (1908–1909) paid special attention to these "sporoids," which he often found enclosed in large, hypertrophic cells. The same occurrence, i. e., the replacement of endospore formation by the development of gonidangia, has been already reported by *Weibel* in 1888 in regard to asporogenous anthrax bacilli, and by *E. Klein* in 1899 as a result of his studies upon *B. cadaveris sporogenes*; though, again, in the opinion of the latter author, these giant cells were "probably involution forms." *P. Eisenberg* (1908) noticed that asporogenous strains of *B. anthracis, tumescens, Megaterium,* and *ramosus* occasionally may exhibit a comparatively high resistance; a temperature of 90° C. was endured in his experiments for 5–15 minutes. He assumes that the capsules of *B. anthracis,*

and in the other cases "Ausnahme-Zellen," are to be made responsible for this result. That the latter have been regenerative bodies is very probable. According to *Garbowski* (1907*b*) the secondary colonies of *B. luteus sporogenes Smith* et *Baker* produced, instead of endospores, irregular forms, which were declared to be vegetative cells, but which evidently also have been in reality gonidangia and regenerative bodies. This conclusion is supported by the fact that *Preisz* (1904) found the irregular, mostly round or pear-shaped cells, present in the secondary colonies of otherwise spore-forming bacilli, to be fairly resistant; and earlier findings by *Chauveau* and *Phisalix* (1895), as well as *Henri's* more recent observations, leave no doubt that true regenerative bodies may be produced in large numbers by asporogenous strains of endospore-forming bacilli. Furthermore, it has been ascertained by *Olsen* (1897), *Cozzolino* (1900), and by *Peklo* (1910) that club-shaped cells may produce one endospore each, instead of becoming normal gonidangia. All these facts together may serve as additional evidence concerning the close relationship existing between gonidia, regenerative bodies and endospores, and in regard to the possibility of mutual replacement in the one or in the other direction. How the resistance gradually increases, when gonidia and regenerative bodies revert again to endospores, has been already studied to some extent by *Phisalix* (1892). Addition of blood to broth cultures of an asporogenous Anthrax strain was found to be very useful for promoting this process, but just as the bright "pseudospores" (gonidia) were quickly killed at 65° C., so the first new spores also withstood this comparatively low temperature only for a few minutes. Later, however, the usual high resistance was regained.

That the form and also the resistance of the endospores is by no means so constant, as is assumed by some authors needs hardly to be emphasized. With regard to anaerobic bacilli these facts have been made clear by *Hibler* (1908), but the same holds true with the aerobic bacilli. An average or "typical" form and resistance may, of course, be calculated; these, however, are again more or less dependent on the conditions of the experiment. That the resistance of the round terminal spores of the Tetanus-Putrificus group is generally distinctly lower than that of the regular oval endospores, as produced by *Bac. mesentericus, subtilis,* etc., and that, in addition, "failures" are much more frequent with the former than with the latter, once more confirms our view that such terminal spores should be better separated from the endospores, and find their place as exospores between regenerative bodies and endospores.

The germination of the endospores has also been accepted as being quite constant, and has been used accordingly by some authors, like *Migula,* as a means of classifying the spore-forming bacilli. That this assumption was not correct, and *Migula's* procedure therefore not well founded, has been shown by *Caspary* (1902). The same holds true, of course, with regard to such minor details, as the presence or absence of a special membranous capsule around the spore, to which occurrence great importance has been attached in the case of Clostridium Pastorianum and related forms of the Amylobacter group. The careful studies of *Bredemann* (1909) have decided this question.

That endospores sometimes may germinate while still enclosed within the parent cell, as was observed, e. g., by *Garbowski* (1907*b*) with *B. asterosporus,* furnishes an interesting counterpart to the analogous upgrowth of the gonidia retained within the parent cell or gonidangium, as was discussed on page 128.

Not only the mode of germination of the endospores, but the fact itself is by no means so constant as is often presumed. Many endospores not only refuse to germinate when tested, they even dissolve entirely and pass over into the symplastic stage, just as is done by many gonidia and regenerative bodies (see Chap. III). Whether they are also able to multiply by budding or by fission has never been studied, and the mere assumption that such a case might be possible is quite liable to be rejected as simply absurd by the well-established bacteriological dogmatism. However, as the complete dissolution of these apparently very solid forms is not difficult to ascertain, so it is also to be expected that positive results may be secured occasionally in the last-named direction. I have often seen round darkly staining buds attached to liberated endospores, looking exactly like the regenerative bodies growing at the side or at the end of the vegetative cells. The sprouting of young exospores from Azotobacter cells

containing at the same time endospores, as shown in figure 69 on Plate VI, is another fact to be kept in mind in this connection. *Maher* (1915) speaks of a breaking up of Subtilis spores into "cocci" or "vital granules," and as early as in 1878 it was reported by *Ewart*, that he saw what he calls Anthrax "spores" divide themselves into 2 and 4 parts, while others germinated directly. It is more probable, as was said on page 93, that these spore-like bodies, which have also been observed by *E. Klein* (1883) and more recently by *Růžička* (1908), have been regenerative bodies or microcysts. Nevertheless, they also might be considered to have been rudimentary endospores, still showing some of the features characteristic for the less resistant reproductive organs. It is likewise to be admitted, that not the well developed "ripe" endospores are inclined to enter the symplastic stage, but that this is more a kind of subterfuge for rather weak endospores, which otherwise would be complete "failures."

(4) ARTHROSPORES AND MICROCYSTS.

The formation of arthrospores, i. e., the segmentation of the vegetative bacterial cell and the transformation of these segments into fairly resistant reproductive organs, seems to have been first observed by *Van Tieghem* (1879*b*) with a spirochaete found in oysters. Soon after *Zopf* (1881) and later *W. H. Hoffmann* (1912), as well as *Gross* (1912), reported upon similar findings. Some characteristic drawings made by the last-named author have been reproduced as figure 63 on Plate O. *Kurth* (1883) studied the same process with *B. Zopfii*, where he saw each rod produce two arthrospores. *Hueppe* (1885), who like *DeBary* (1884) believed the formation of arthrospores to be very widespread among the bacteria, also accepted the breaking up of the rods into coccoid resistant bodies as the characteristic feature of this process. Both authors, however, have used the term in a rather loose manner; regenerative bodies, as well as microcysts, have also been called by them arthrospores. The same holds true with regard to *Zopf* (1892), who ascribed, for instance, arthrospores to his *Bact. vernicosum*, merely because he observed a slightly increased resistance, which, of course, may just as well have been due to the presence of regenerative bodies. A good example of typical arthrospore formation has been contributed by *Matzuschita* (1902), when he described his protean bacillus from air. His drawings, reproduced as figure 5 on Plate B, show clearly side by side formation of gonidia and their upgrowth within the gonidangia, the presence of lateral regenerative bodies, the production of arthrospores, and the transformation of whole cells into microcysts. Most regular and characteristic, however, is the arthrospore formation with the Actinomycetes. *Gasperini* (1889), *Domec* (1892), *Kedzior* (1896), *Doepke* (1902), *E. Levy* (1902), *Gilbert* (1904), *Lehmann* and *Neumann* (1912, p. 622) have furnished descriptions of this process. Most typical is the dividing up of the short side branches of aerial hyphae into the coccoid spores, sometimes also called conidia, in accordance with mycological nomenclature. In the long threads the development of reproductive organs often stops with the formation of the gonidia, which then slip out, leaving the empty sheath behind them. This is still more frequently the case with the Mycobacteriaceae (see p. 124). Some of the papers upon tubercle bacilli, however, also contain reports on genuine arthrospore formation. And the slight differences recorded by the numerous authors dealing with "fragments," "spores," and "granules" of the tubercle bacilli, are undoubtedly caused in part by the fact that, on account of incomplete observations upon the manner in which these bodies were formed, it could not be ascertained exactly whether the round forms seen and tested have been gonidia or regenerative bodies or arthrospores.

The round thick-walled resting cells of the genus Myxococcus have also been repeatedly called arthrospores. But as most authors who studied the subject have reported that the whole cell contracts itself, forming one resting body, the term microcysts seems to be preferable. It is true that it has been observed in some cases, for instance by *Kruyff* (1908), that the rods first divide themselves, and it is to be admitted, as was said on page 123, that such occurrences may be also considered to represent arthrospore formation, but it seems best to place them in an intermediate position, connecting arthrospores and microcysts.

The form of the arthrospores is, according to their mode of formation, not always exactly spherical or ovoid, but more of cubical shape, and as the thickening of the cell wall is most

characteristic for this process, the staining reaction does not show any, or at least not much, alteration, compared with that of the vegetative cells.

Germination of the arthrospores of spirochaets has been studied first by *Van Tieghem* in 1879, while more recently *Gross* (1912–1913), as well as *W. H. Hoffmann* (1912), were unable to observe this process again. Positive results have been also recorded by *Kurth* (1883) with his *B. Zopfii*, and by *Gasperini* (1889), *Domec* (1892), *Lachner-Sandoval* (1898), *Feistmantel* (1902), *E. Levy* (1902), *Gilbert* (1904), and others in regard to Actinomycetes. These findings invalidate a statement made by *Jordan* (1909), p. 407; 1916, p. 463), that the coccoid bodies produced by Actinomycetes are not "in anywise related to the normal reproduction of the species." Not infrequently two to four young threads break forth simultaneously, creating a picture very similar to that shown of *B. coli* in figure 200 on Plate XV. The membrane of the germinating arthrospore seems to be used again, if not always so, at least in most cases.

Multiplication as such has been never recorded with genuine arthrospores.

The resistance of arthrospores has been always found to be much greater against drying than against heating, although in this direction again fully developed arthrospores are clearly more resistant than vegetative cells. According to *Kurth* (1883) the dried rods of *B. Zopfii* died after 5–7, the arthrospores after 17–26 days, but heating experiments revealed no difference. Abnormally high resistance was recorded by *Kedzior* (1896) for a thermophilic actinomyces, whose spores are said to have withstood 100° C. (steam) for 3½–4 hours. *Neukirch* (1902) found 5 minutes at 70° C. to be the limit; *Feistmantel* (1902) fixed the death point for spores of "Streptothrix farcinica" at 60° C. for 15 minutes. *MacCallum* (1902) noticed that young cultures of *Actinomyces asteroides* were killed at 65° C. within 5 minutes, while older ones endured 65° for 30, 68° for 5–10 minutes. The vegetative cells of *Actinomyces thermophilus* died according to *Gilbert* (1904) at 65° within 5 minutes, but the spores withstood 70° C. for more than an hour. Old dry cultures of *Actinomyces violaceus*, grown on straw and practically completely transformed into spores, were found by *Berestneff* (1907) to be still alive after more than 10 years. *Lehmann* and *Neumann* (1912, p. 623) state that vegetative cells of Actinomycetes are killed at 60–65° C., whereas the arthrospores endure 75–85° C. for 5 or 3 minutes.

The formation of a microcyst, i. e., the transformation of a whole vegetative cell into one usually relatively large resting body, is characterized in most cases by a swelling up and rounding of the cell, followed by a more or less considerable thickening of the cell wall. With the curved forms, especially with spirochaets, a coiling up of the body initiates the process. Microcyst formation seems to have been first seen with Streptococci. As early as in 1876 *Salomonsen* reported that Streptococci, which otherwise did not produce resistant cells, furnished great numbers of them when kept in blood at 40° C. Soon afterwards *Van Tieghem* (1879*c*) published his first illustrated description of *Leuconostoc mesenterioides*, whose "spores" were shown to be analogous to the heterocysts of the Nostocaceae, in which group of organisms Leuconostoc itself was later placed by *Van Tieghem* (1884, p. 1108). Its "spores" were now called "kystes." When studying his *Micrococcus ochroleucus*, *Prove* (1887) noticed that the cells, whose normal diameter was 0.5–0.8μ, sometimes increased to 1.6–1.8μ diameter and became more resistant against heating, as well as against staining. Some of the large dark cells visible in our photographs of *Streptococcus lactis* (Plate I, fig. 11) and of *Sarcina flava* (Plate II, fig. 15) look very much as if they had also been microcysts, but no special tests upon germination and increased resistance have been made so far. The drawings of the acetic acid bacteria, made by *E. Chr. Hansen* (1879), show within the chains some large thick-walled cells, which *Hansen* considered to be possibly "spores." (See fig. 15 on Pl. E.) Likewise, the pictures of the "proteusartige Luftbacillus," drawn by *Matzuschita* (1902; see fig. 5 on Pl. B), leave hardly any doubt that microcysts were also formed by this species. An excellent illustration of the same process, as seen with spore-forming bacilli, has been furnished by *A. Meyer* (1901); it was reproduced as figure 64 on Plate O. The drawing made by *E. Klein* (1883) of the round forms of *B. anthracis*, which has been shown as figure 21 on Plate F, furnishes an interesting counterpart. The thick-walled large cells of Azotobacter are equally typical microcysts. *H. Fischer* (1905), *Krzemieniewski* (1908), and especially *Prazmowski* (1912, p. 162) have studied them fairly thoroughly.

Vibrio proteus has been seen by *Firtsch* (1888) to coil up occasionally, as it is rather frequent with spirochaets, according to the observations made by *Breinl* and *Kinghorn* (1906), *Prowazek* (1906*b*, 1907*a*), *Breinl* (1907), *Schaudinn* (1907), *Gonder* (1909), *Karwacki* (1911), *Wolbach* and *Binger* (1914), *Inada* et al. (1916), and others. Unquestionably not all of these coiled forms develop actually to regular microcysts. The drawings made by *Prowazek* (1907*a*, original fig. 8*b*), which are reproduced as figure 74 on Plate P may illustrate this possibility, while some other sketches, published by *Inada* and his collaborators (1916, original figs. 71 and 72) and reproduced as figure 75 on Plate P, probably are to be accepted as showing the formation of genuine microcysts.

Germination of microcysts has been recorded with those produced by cocci and by Azotobacter. *Van Tieghem* (1879*c*, 1884) saw that the "kystes" of Leuconostoc when still inclosed in the chain germinated laterally and the membranes of the microcysts were left behind by the young cocci. The analogous behavior of the heterocysts of Nostoc and of other Cyanophyceae has been described by *Brand* (1901). Germination of the microcysts of Micrococcus ochroleucus has been observed by *Prove* (1887). *H. Fischer* (1905) reported that the germinating Azotobacter left no empty membrane behind, but *Krzemieniewski* (1908), *Prazmowski* (1912), and *D. H. Jones* (1913) recorded opposite results.

In the same manner as some of the vegetative cells increase in size and become gonidangia, so also microcysts may occasionally undergo a similar change, and they, too, may either liberate a number of gonidia, or these may reproduce new vegetative cells while still inclosed within the microcyst. The liberation of the gonidia seems to be the rule with the microcysts of spirochaets (*Breinl*, 1907); direct germination apparently never has been observed in this case. The microcysts of streptococci not infrequently break up into 3 or 4 parts, each of them acting as a new vegetative cell. *Babes* (1908) probably was the first to give an account of this interesting occurrence. If such a cyst remains within the chain, it may act as a very conspicuous starting point for branches, as was noticed by *Vincent* (1902). The early report of *E. Klein* (1883) upon what has been at least in part microcysts of *B. anthracis* also refers to their dividing into 2, 3, or 4 parts, each of which proved to be able either to multiply as a round budding vegetative cell, or to grow up again to a normal rod. The drawings made by *Matzuschita* (1902) from his protean bacillus from air, reproduced as figure 5 on Plate B, shows also some large round cells, looking like microcysts, which clearly exhibit the same mode of fission. More recently *Hort* (1917*b*) noticed that the "giant cells" of Meningococcus may either become gonidangia or divide themselves into 3 or 4 equal parts.

Concerning the resistance of the microcysts very little is known at present. Similar to the arthrospores, they are evidently more apt to withstand the influence of drying than that of heating. However, in a few cases *Prove* (1887) was able to record a surprisingly high resistance; some of the microcysts tested by him are said to have endured 100° C. for more than one-half hour. *Baumgarten* (1890, p. 295) mentioned that old cultures of staphylococci were not always killed, when kept at 99° C. for 15 minutes, and *A. C. Abbott* (1912) succeeded in selecting especially vigorous strains of *Staphylococcus aureus* by keeping the original culture for 5–20 minutes in fairly strong antiseptic solutions (0.1 per cent $HgCl_2$, 0.75 per cent phenol or saturated Na_2CO_3). *Holman* (1914) noticed that in one case streptococci were not even killed when kept three times for 20 minutes in the Arnold apparatus, a result which evidently must be attributed to the presence of protecting albuminous substances in the substrate. Special experiments upon the heat resistance of the microcysts of Azotobacter, *Bac. anthracis* and of related species apparently have not been made so far. A rather considerable resistance against drying, however, has been repeatedly observed with the first-named organism.

(*d*) GONIDIA AND FILTERABLE VIRA (CELL INCLUSIONS, APHANOZOA, ETC.)—GONIDIA AND HETEROGENESIS.

The size of the bacterial gonidia shows wide variations, especially when they have grown within a gonidangium. With the smaller species the diameter is usually 0.1–0.3 μ. Therefore, a more or less considerable number of gonidia is able to pass Chamberland, Berkefeldt, and similar bacteria filters, and when transferred to a suitable medium, such a filtrate, though freed

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from all bacteria, may still cause an effect on account of the gonidia present therein. This possibility makes the filterable gonidia an important subject in connection with the study of filterable vira, certain cell inclusions, so-called aphanozoa, chlamydozoa, etc. Some of these may, indeed, belong to the protozoa; but there is no reason why the same assumption should be accepted as the only working hypothesis in all cases. In fact, several observations are already available, which make it certain that sometimes bacterial gonidia, too, may play an important part, and it is very probable that they will win in importance, as soon as more attention is centered upon this point.

General reviews of the whole subject have been published by *Prowazek* (1907), *Lipschütz* (1909), *Loeffler* (1911), *Doerr* (1911), *Wolbach* (1912), *Fontanel* (1913), and others. According to the first-named author the small bodies concerned are less than 0.25 μ in diameter, of globular shape, occurring singly, in pairs, in chains or small clumps, difficult to stain, usually best with *Giemsa's* method, and fairly resistant against physical and chemical effects. In addition *Fontanel* has pointed out that they are probably all motile. All these characters would fit the filterable bacterial gonidia: size, shape, motility, staining qualities, as well as increased resistance, are the same. That especially glycerin is a good preservative for gonidia, as it is for filterable vira, has been already ascertained by *Neelsen* in 1880, and more recently by *Mathers* (1917). With regard to alcohol analogous results have been obtained by *Iwanowski* (1899).

The development within the cells of the host as "cell inclusions," "Kern-Kappen," etc., has been often assumed as indicating the protozoal nature of the intruders. But already in 1889 *MacFadyean* reported upon the interesting fact that the small "cocci" (gonidia) produced by Actinomyces invade the animal cell, sometimes even the nucleus, and develop therein. The gonidia of spirochaets were seen by *Balfour* (1911 *b*), *Ross* (1912), and others, to behave in the same manner. And *Dutschenko* (1914) was able to ascertain that smallest inclusions, found by him within the red blood cells of rodents, which they destroy, and which therefore at first were considered to be some protozoa related to Theileria parva, developed, after being liberated, in the blood to bacteria, similar to those of the plague.

That gonidia, and sometimes regenerative bodies, too, may occur within the mast cells, has been mentioned on page 111. As *Herzog* (1913) has pointed out, it still remains to be studied, whether the "eosinophilic" granules, which are present in blood cells, are actually cell products or bacterial gonidia. That the latter are much inclined to grow as such, and to replace the bacteria within the body, has been pointed out by *M. E. Abbott* (1900) and others. The fact, that thus far only in a few cases development of normal bacteria cells has been obtained from these filterable coccoid bodies, does not exclude the possibility that improved methods will secure positive results also in other cases. As far as filterable vira have been cultivated as such, their behavior did not differ from that shown by cultures of filterable gonidia.

The organisms of vaccine and variola, classed by *F. Cohn* (1872 *a* and *b*) somewhat prematurely as *Micrococcus vaccinae*, were declared by *Calkins* (1904) to belong to the Microsporidia; but all his findings can be just as well accepted as descriptions of bacterial gonidia, regenerative bodies, and symplasm. Distinctly more in favor of the protozoa hypothesis are the results obtained by *Howard* and *Perkins* (1904), while the various communications made by *Prowazek* (1905, 1906 *a*, 1907 *c*) upon "Initialkörper" and Chlamydozoen" leave the matter again entirely in doubt. The findings of *Bonhoff* (1905) upon what he called *Spirochaeta vaccinae*, seem never to have been followed up; they were very similar to results obtained in various spirochaetoses. That the causative agent is filterable has been shown by *Siegel* (1905 *a*) and by *A. Negri* (1906). The cultures made by *Siegel* (1911) of his *Cytorrhyctes vaccinae* would suggest relations to some Micrococcus. However, no conclusive results have been secured.

The various coccoid bodies found by *Nencki, Sieber* and *Wijnikewitsch* (1898) to be connected with "Rinderpest" also failed to exhibit any sign, which would be strictly against their bacterial nature.

The small motile globules first grown by *Nocard* and *Roux* (1898) from pleuropneumonia of cattle, seem to have been the gonidia of a pleomorphous bacterium, described by *Bordet* (1910), by *Borrel, Dujardin-Beaumetz, Jeantet,* and *Jouan* (1910) under the name *Asterococcus*

mycoides, and by *Martzinowski* (1911) as *Coccobacillus mycoides peripneumoniae*. Confirmative reports are still outstanding; and *Kallert* (1911) is of the opinion that colloidal substances from the serum have been mistaken for organisms.

After *Dorset, Bolton*, and *McBride* (1905) had ascertained that hog cholera is caused by a filterablev irus, *Lourens* (1907) showed that *Bact. cholerae suum* is able to produce filterable "granules," which were found to be able to reproduce the bacilli in the animal, but not in the cultures. They were, therefore, declared to be the primary, the bacilli the secondary cause of the disease. *Hübner* (1908) contested these observations strictly, as did *Uhlenhuth, Xylander, Hübner* and *Bohtz* (1908–1909), who confirmed and extended the findings of the American authors, not only with regard to hog cholera, but also concerning swine plague. The multiplication of the filterable virus as such was especially studied by *Pfeiler* and *Lentz* (1913). *Rüther* (1910), on the other hand, is of the opinion that the granules present in the infectious filtrate are produced by spirochaets, which were seen to be present in blood, urine, and in the organs of diseased, but not in healthy hogs. After 10 days they also reappeared in the filtered virus, and their reproduction from the filterable granules is reported to have been observed on solid substrates, too. The granules were found in great number in lice and intestinal parasites (nematodes and others), to which the author ascribes, therefore, an important rôle in transmitting the disease. Sometimes the spirochaets were seen to break up into small rods, looking like *B. septicaemiae* or *influenzae*. Very similar results have been obtained by *King* in cooperation with *Baeslack* and *Hoffmann* (1913) with a *Spirochaeta suis*, which again was found only in diseased hogs and was seen to break up into filterable infective granules. *Healy* and *Gott* (1916) were able to grow the filterable forms as such in 1 per cent glucose broth, to which ground mesenteric glands of hogs had been added, and *Proescher* and *Seil* (1917) described anew the small coccoid bodies present in endothelium cells, blood, and urine.

Trachoma, as well as blennorrhoea non gonorrhoica, are caused, according to *Halberstädter* and *Prowazek* (1909), by the Chlamydozoa discovered by them. As *Heymann* (1909) has pointed out, however, only the "Kern-Kappen" are to be considered of diagnostic value, while single and double granules were declared by him to be present in various affections of the conjunctiva. On the other hand, extended studies of this subject led *Herzog* (1910) to the conclusion, that the so-called trachoma bodies should not be connected with protozoa, but are formed by "micro-gonococci," which are produced by "macro-gonococci." *Böing* (1912) was not willing to accept any of these findings as being correct, and also *Noguchi* and *Cohen* (1913) at first were only able to isolate and cultivate anaerobically small coccoid bodies, whose cultures showed all stages of the so-called inclusions, but did not give definite results in inoculation experiments. *Herzog* (1913), however, furnished further proof concerning the rôle played by the minute "involution forms" (gonidia) of the gonococci; an interesting picture, presenting these smaller and larger, globular and dumb-bell-shaped bodies, has been reproduced as figure 202 on Plate XVI (from original fig. 5 on Pl. III). It should be compared with figure 2 on Plate A. The matter was brought beyond doubt by the extensive investigations made by *Williams, Wilson* and *Gurley* (1914). Trachoma inclusions are, according to these authors, "simply intracellular nests of growing bacteria"; besides the gonococcus a hemoglobinophilic bacillus was found to be able to produce in cultures, as well as in the eye, all forms described by *Prowazek*, especially "dense clumps of extremely minute and irregular coccoid forms." A second contribution by *Noguchi* and *Cohen* (1915 added some interesting data, suggesting analogous relations existing between the Koch-Weeks bacillus and cell inclusion conjunctivitis.

With regard to lyssa *Babes* (1907*c*) has pointed out that while the so-called Negri bodies are not always visible and probably represent merely cell products, very small granules, which stain like bacteria, are constantly present. *A. Negri* (1909), however, maintained, that the cell inclusions be parts of the life cycle of a protozoon, *Neurorrhyctes hydrophobiae*. The standpoint taken by *J. Koch* and *Rissling* (1910) is more that of the first-named author, and *S. R. Klein* (1911) reached the conclusion that rabies is to be considered as a very acute streptococcal infection, and the Negri bodies as remnants of these streptococci. Staining

experiments misled *Tanakamuru* (1913) to assume, the granules present in rabietic brain to be merely lipochrom and degeneration products of the gangliar cells. *Noguchi* (1913), as well as *Williams* (1913), were able to cultivate the virus as such. They both think that the bodies grown looked like protozoa, not like bacteria; but the photographs made would equally fit the appearance of bacterial gonidia and regenerative bodies.

From scarlatina filterable, motile granules have been obtained by *Siegel* (1905 *b*), who classes them as *Cytorrhyctes scarlatinae* among the protozoa, while *Bernhardt* (1911) has pointed out, that the cell inclusions visible are similar to those seen in trachoma, and this holds true also with regard to the fine filterable granules, which are often dumb-bell-shaped. That they may be the gonidia of the streptococci, which are always present as "secondary invasion" in scarlatina as in measles, has become very probable by *Hort's* studies (1915–1917).

Poliomyelitis is another case where it seems to be very probable that the filterable small bodies first obtained by *Flexner* and *Noguchi* (1913) are gonidia of streptococci. After they have become adapted to artificial substrates, they behave very much like small streptococci, according to the data furnished by *Flexner*, *Noguchi* and *Amoss* (1915). That, however, the small forms are, in fact, parts of the life cycle of a polymorphous Streptococcus, has been first proclaimed by *Rosenow*, *Towne* and *Wheeler* (1916), and it was soon afterwards confirmed by *Nuzum* and *Herzog* (1916). These, as well as the further contributions by *Rosenow* and *Towne* (1917), *Mathers* (1917), *Mathers* and *Howell* (1917), *Rosenow* and *Wheeler* (1918), *Rosenow*, *Towne* and *Hess* (1918), leave hardly any doubt that it is also in this case the filterable gonidia, which act as the specific virus. *Amoss* (1917), as well as *Bull* (1917), have contested *Rosenow's* and *Nuzum's* results, but their own experiments can not be accepted as convincing negative proof, especially when the peculiar staining reactions, as well as the characteristic cultural behavior, of the filterable gonidia are duly considered. *Rosenow* and *Towne* are undoubtedly right when they point out that the whole subject concerning the filterable vira needs a comprehensive study from these new standpoints.

The aphthe virus has been classed by *Siegel* (1905 *a*) as a *Cytorrhyctes aphtharum* in the neighborhood of *Cytorrhyctes vaccinae*, but later experiments (1910) led him to the belief that this Cytorrhyctes is a type of growth of a micrococcus. Further investigations (*Siegel*, 1912) strenghtened this view; his photographs are exactly of the same type as those made by *Rosenow*, *Nuzum* and by *Mathers* of the poliomyelitis germ. Pictures published by *Betegh* (1911) of what he considers to be the causative agent of foot-and-mouth disease, are very similar. *Siegel's* as well as *Betegh's* claims have been refuted by *Wehrle* and *Zwick* (1913) and by *Kallert* (1913). A reply was published by *Siegel* (1913). The problem needs further unbiased study, as was emphasized by *F. Winkler* (1906).

As causative agent of syphilis a *Cytorrhyctes luis* has been introduced by *Siegel* (1905 *c*), which was accepted by *Leuriaux* and *Geets* (1906) as the granular form of *Spirochaeta pallida*. The important rôle played by the gonidia in other spirochaetoses has been repeatedly emphasized. *Rüther's* and *King's* reports upon the granules of *Spirochaeta suis* were quoted above, those made by *Breinl* (1907) upon the filterable gonidia of *Spirochaeta Duttoni*, by *Balfour* (1911 *a* and *b*) upon *Spirochaeta granulosa*, and by others have been discussed on pages 105–106. *Wolbach* and *Binger* (1914) pointed out correctly that sometimes errors may be caused by spirochaets passing the filter, just as is done occasionally by other bacteria; but the first-named author's statement (*Wolbach*, 1915), "that there is no evidence of spirochaets multiplying by any other method than single fission," is not in accordance with certain observations, and that in his experiments the granules did not multiply as such, does not invalidate the fact, that under suitable conditions all bacterial gonidia act in this manner. *Balfour's* discovery concerning the higher resistance of the "infective granules" against salvarsan and the importance of this finding in regard to chronic spirochaetosis have been mentioned on page 131.

The widely varying observations upon typhus exanthematicus may be accepted as another instance where the study of the presence and action of bacterial gonidia will help solve the problem. The diplococcus, described by *Rabinowitsch* (1909), as well as the pleomorpho

organism isolated by *P. Th. Müller* (1913), whose pictures have been reproduced as figures 22–24 on Plate II, or the equally pleomorphic anaerobic bacillus discovered by *Plotz, Olitsky* and *Baehr* (1915), may all act either as such or by means of their gonidia. *Hort's* (1915–1916 *a*) experiments have already brought much light in this direction.

With meningitis the situation is quite similar. Here again, according to *Hort* (1916 *a*), the micrococci themselves are important as a "danger signal," that the true infective agent, their filterable gonidia, may be present. The fundamental importance of these meningitis investigations, made by *Hort* and his collaborators (1915–17), has been justly emphasized by *Adami* (1916), who also pointed out that besides to meningitis, typhus fever, scarlatina, and hog cholera the same principle may apply to tuberculosis. That, indeed, filterable gonidia are produced by *B. tuberculosis*, too, had been demonstrated already by *Fontes* (1910).

That in common colds once more filterable gonidia are of etiologic significance, is practically beyond doubt. The anaerobic organism isolated by *Tunnicliff* (1913–1915) from the nose, as well as *Micr. catarrhalis*, and perhaps other bacteria, too, again seem to be less important directly than indirectly by their producing infective, partially filterable gonidia. What *Kruse* (1914) named *Aphanozoum coryzae*, the virulent filtrate causing the cold, has been cultivated as such by *Foster, jr.* (1917). Morphology and staining reactions of the smaller and larger budding bodies, which the author compares with *Flexner's* globoid poliomyelitis germs, are exactly those of gonidia and of regenerative bodies.

That the virulence of the gonidia may be more or less different from that shown by the vegetative cells, from which they originate, is not surprising. Of equal interest, however, is the possibility, that distinctly antagonistic activities may be displayed by the parent cell and its reproductive organs. *Almquist* (1911) obtained, when studying the growth of filtered gonidia of *B. typhosus*, occasionally instead of the usual, very scant development, a thick yellowish layer on lactose agar, formed by small immotile oval forms, which were not pathogenic, but whose sera agglutinated the typhoid bacilli. That these peculiar organisms have been no contamination has become certain by further investigations made by *Almquist* (1917), which in no case gave an upgrowth of normal typhoid bacilli from the filtrate, while in 10 per cent of the tests the same "*Bact. antityphosum*" was obtained, which remained stable for 7 years, and which on account of its behavior in the agglutination and in the *Pfeiffer* test is believed to be a "mutation" of *B. typhosus*. *Herelle* (1917) also reports to have isolated from feces and urine of dysentery convalescents an "invisible" microbe of antagonistic character, which did not grow on any substrate, except in the presence of dysenteria bacilli killed and solved by heating. Similar results, though not quite so clear, were obtained by the same author in studies upon paratyphoid.

The possibility that all bacteria, perhaps with the only exception of the large trichobacteria, may produce filterable gonidia, makes the conclusion inevitable, that they must be present quite generally in nature, as well as in the laboratory. In fact, the omnipresence of "ultramicroscopic" germs of bacteria has been already considered by *Burdon-Sanderson* in 1871, and more recently by *Gaidukov* (1906); but this hypothesis has been refuted by *Molisch* (1908) and by *Cano* (1909). The former author points out that neither he nor anybody else had ever obtained cultures of "ultra-microörganisms," and the latter recorded nothing but negative results when he tested the filtrates of many different substances under the microscope, in cultures, or in the animal test. These negative findings, however, are by no means decisive. As is the case with the filterable vira, also the other, not pathogenic filterable gonidia produce in or on the substrates used in the laboratories—provided that they grow at all—such a very scant growth that it can be as easily overlooked as their presence under the microscope. The extremely thin and restricted dewy layer on solid media, or the very slight cloudiness in liquid substrates, seems to be all what can be expected. But as at least in some cases a renewed development of larger forms has been secured, it is to be expected that more positive results will be obtained, when the conditions allowing such upgrowth will be better known, and especially if the important rôle played also in this case by the symplastic stage, will receive adequate consideration. That positive results have been obtained more frequently within the animal than in cultures agrees well

with the fact that genuine plasma, not changed by heating, evidently greatly favors such upgrowth as is clearly indicated by the observations to be presently discussed.

The knowledge of the participation of the gonidia in the life history of the bacteria throws a very interesting light upon some facts, which have been accepted so far by several authors as stringent proof of the possibility of heterogenesis. It has been mentioned already (on p. 14) that some years ago *Dunbar* (1907), whose experience in doing bacteriological work can not be questioned, published a book wherein he gave many facts apparently proving that all kinds of bacteria may be produced by the same species of algae, and that this book was accepted by authors like *Pringsheim* as an attempt to undermine the whole science of bacteriology. If the general knowledge of the literature would be better as it usually is, it had at once become evident, that *Dunbar's* results are practically identical with those recorded by many earlier authors, who all found, that within dying or dead cells of algae, fungi or other organisms, bacteria may develop from smallest granules, which microscopically can not be distinguished from the cell granules themselves.

Dujardin (1841, p. 93) mentions that it has been the opinion of *Müller, Dumas, Gleichen,* and other authors, at the end of the eighteenth and at the beginning of the nineteenth century, that the organic residues of plant and animal life dissolve themselves into "globules élémentaires," which by transformation may become "infusoires." According to *Fokker* (1887 *a*, p. 3), *Buffon* and *Needham* assumed that the living molecules after the death of plants and animals may continue their existence as such and eventually build up new microörganisms. *Perty* (1852), *Pouchet* (1863), and *Trécul* (1865–1867) stood practically on the same heterogenetic standpoint, and the victory attained by *Pasteur* in regard to spontaneous generation had in fact not much influence in this direction. That life can not begin anew was soon generally admitted, but the theory of heterogenesis still found many defenders, and as long as the existence of the bacterial gonidia is not taken into account is, indeed, invincible.

The detailed description given by *Trécul* (1865–1867) of the upgrowth of Amylobacter within closed dead cells from very small granules, "les derniers molécules vivantes de protoplasma," fits remarkably well to the results recorded by *Dunbar*. The same holds true concerning the findings made by *Karsten* (1869) together with *Harz*, who by continuous direct microscopic observations ascertained that within cells of yeasts and of other fungi, but only when their vital activity had come to a standstill, "micro-gonidia" may develop, which later either internally or externally may grow up to "Vibrionen":

> Sehr überzeugend sieht man diese Entwicklungserscheinungen der endogenen Zellchen zuweilen an einzelnen Gliedzellen von Pilzmycelien, die zwischen andern, welche gesund verbleiben und sich normal entwickeln, erkranken (p. 29).

An interesting drawing made by *Karsten* (1869) is reproduced as figure 76 on Plate Q (from original fig. V). The development of small rod-like bacteria within a Rhizopus sporangium, and the upgrowth of various forms from the minute "micro-gonidia" is fairly well discernible.

The otherwise rather faulty observations made by *Hallier* (1866–1896) and by *Lüders* (1866) have been correct in so far as these authors, too, have watched directly the transformation of smallest granules within dead cells of fungi into bacteria, but it was, indeed, an astonishing logical mistake, when *Hallier* still in 1895 (p. V) tried to defend the following absurd conclusion:

> Die winzigen Zellbildungen, welche *Nägeli* unter dem Namen der Spaltpilze zu einer Familie zusammengestellt hat, sind keine vollständigen Gebilde, sondern Erzeugnisse des Plasma verschiedener Pilzgruppen. Die *Nägelische* Familie der Spaltpilze ist also aus dem System zu streichen.

The voluminous contributions made by *Bastian* (1872–1914) to the theory of heterogenesis become also quite interesting, when read with some knowledge of the existence and the behavior of the bacterial gonidia and, in addition, of the symplastic stage of bacterial life, as will be discussed in Chapter III. The "newly evolved specks of living matter" now lose at once their mysterious character.

The "microzymas" of *Béchamp* (1883) present a similar case. His drawing reproduced as figure 77 on Plate Q (from original fig. 4 on Pl. I) show formation and liberation of gonidia by

long rods about as clearly, as it was pictured, for instance, by *Billroth* in 1874 (see fig. 45 on Pl. L) or 40 years later by *Meirowsky*. (See Pl. XIV). It will be justly doubted, however, that *Béchamp* was right when he stated (p. 628):

Les seuls éléments anatomiques non transitoires de l'organisme qui persistent après la mort et qui évoluent pour former des bactéries, sont les microzymas.

But in view of the observations mentioned above, it is already more easily to be understood, when he says (p. 143):

. . . que les microzymas sont de ceux qui produisent aisément des bactéries.

And when he points out (p. 473) that the microzyma is not by itself a bacterium, but is related to it in the same manner as a spore to a mold, and (on p. 839) that the bacterium is able to produce again "microzymas" he evidently comes very close to the truth. That bacteria easily develop from the "microzymas" in dead plant cells, blood corpuscles or fibrine, while other substances, for instance the white of the egg, did not give such a "transformation," is also in full agreement with the findings of other investigators.

Engler (1882) reported, that he not infrequently saw small bacteria develop within dying cells of a large Beggiatoa, though he did not assert, of course, as did *Wigand* (1884), that they were formed there by "anamorphosis" of the cell plasma. The latter author thought that he saw all kinds of bacteria grow up from the plasmatic granules within intact plant cells. but apparently no cultural experiments have been made, and it remains, therefore, doubtful, whether these bodies have been real bacteria or only cell inclusions of a similar shape, especially those called chondriosomes.

The numerous experiments made by *Fokker* (1887–1903) to support his "neue Bakterienlehre," which was, however, in fact the old heterogenetic hypothesis, are in so far of greater interest, as the author, late Professor of Hygiene at the University of Groningen, undoubtedly has been well acquainted with bacteriological methods of investigation, and he was able to report that he not only had under his microscope things looking like bacteria, but that he actually cultivated bacteria under conditions which would invalidate the easy explanation of "mere contamination." He confirmed the earlier observations of *Klebs* (1873), *Tiegel* (1874), *Zahn* (1884) and of others, that blood and parts of muscles aseptically won and kept, did not give bacterial growth, but that this became visible within parts of the liver, spleen, and kidneys. Blood alone or diluted with water remained equally sterile, but "hematocyts" appeared and developed to normal bacteria, when small amounts of blood were kept in nutrient solution (slightly acid broth of beef extract and lactose), either at 20°, or 37°, or at 50–52° C. The highest temperature proved to be most suitable. The appearance of these hematocyts, as shown in figure 203 on Plate XVI (reproduced from original fig. I, Pl. I) leaves hardly any doubt that they are regenerative bodies growing up from the gonidia contained within the pale blood corpuscles. That they are first Gram-negative, later gram-positive, that iodine gives them a brown stain, that they are resistant against alkali and acetic acid, and that they apparently multiply by budding, is also in full agreement with this assumption. Further experiments proved that bacteria developed from these round bodies (see fig. 204 on Plate XVI, reproduced from original fig. II on Pl. III); at room temperature a "comma bacillus," at 40° C. yellowish, gelatin liquefying bacteria, and at 52° C. another organism which showed budding and branching, probably an Actinomyces, were obtained. With the "comma bacillus" reproduction by small granules, produced inside of the parent cell, was also observed. *Fokker's* discovery that in cases of anthrax, especially during the first 12–17 hours, no bacilli are visible, but only granules, which stain like the nuclei of the spleen cells, and like the anthrax rods which develop from them, is of interest in this connection, though it does not, of course, support the Dutch author's assumption that it is the granules of the sick spleen cells which become anthrax bacilli. Some others of his findings, especially with regard to "heterogenesis" in milk, will be considered in Chapter III, as the development of regenerative bodies from the symplasm of milk bacteria has obviously caused this faulty hypothesis.

The cell granula theory of *Altmann* (1894) is similar to the earlier ones in so far as he, too, accepts cell granules and microörganisms as equivalent (p. 141), but his standpoint is different when he says (p. 146):

Die Zellengranula lassen sich nicht züchten, sie sterben mit der Zelle ab.

On the other hand, *Hueppe* (1896, p. 31) was not quite right when he tried to discard all positive results by the following statement:

Die Angaben über Bildung von Bakterien aus anderen Zellen und deren Bestandteilen durch Anamorphose des Protoplasma beruhen auf Verwechslungen von Zellkörnern in Milch, Blut, Geweben und von Fibrinausscheidungen und künstlich veränderten Kernbestandteilen mit Bakterien.

Münden (1896–1907) also secured some positive results concerning the development of bacteria from small granules present within plant or animal cells, but his fantastic "cytoblast" and "chtonoblast" hypotheses, founded upon this basis, are certainly of no value whatever. The same holds true concerning the theories promulgated by *J. H. Müller* (1898), who once more had to record negative results, when he tried to "develop" bacteria from living spores of fungi, while dying or dead material reacted differently.

That it is the gonidia of the bacteria which grow up within the cell, making use of the albuminous substances of the dead protoplasm, has been pointed out for the first time and with full certainty by *W. Winkler* (1899). Clean pieces of Hymenomycetes kept in steril wort gave him many "bacterioblasts," which developed new bacteria, just as had been described by *Karsten* thirty years earlier. That, as *P. Ernst* (1902) reported, bacteria often grow in a vertical position and in thick bunches on and around a mycelium, and that *Gaidukow* (1906) found his ultra-microörganisms frequently within closed cells of algae and fungi, is again in complete agreement with the earlier observations.

And it is now easily understood why in strictly pure, single-cell cultures of an alga *Dunbar* (1907) has seen development of different kinds of bacteria in a great number of cases, though extensive controls (over 4,000) proved that these could not be simply explained as contaminations by bacteria. It was again only the dead, not the living, alga cells which gave this growth. Whether the bacterial gonidia had been introduced with the alga, or whether they were, indeed, contaminations from the air, can not be decided. The special tests made with the isolated algae cells on gelatin and on agar are inconclusive, because under such conditions bacterial gonidia do not grow at all, or their growth remains so scant that only special attention in this direction will detect it.

M. E. Abbott's (1900) remark that the small coccoid bodies to be found in liver and other cells may belong to *B. coli* and other bacilli seems to be, indeed, the correct explanation of apparent heterogenesis found at such places; and it may also be considered to be beyond doubt that bacterial gonidia have played their part in the development of bacilli within animal cells, as observed by *Saski* (1907) and by *Portier* (1917).

The behavior of *Anaplasma marginale*, according to *Theiler's* (1910) report, a protozoon causing "gall sickness," seems to be, as far as can be surmised from his and *Sieber's* (1910) description, strikingly similar to that of *Fokker's* "hematocyts." The microscopic picture of these small chromatine granules, growing at the edge of the blood corpuscles and multiplying as such, is exactly like that furnished very frequently by bacterial gonidia. Comparatively large round bodies "studded with chromatine granules" were seen by *Ross* (1912) to occur in cases of spirochaetosis, and they are also by no means rare with *B. radicicola* and *Azotobacter*. Probably they will be found with all bacteria as soon as this subject will be studied more thoroughly.

When the gonidia live within the dead cell, making use of its protoplasm, they naturally become what *Prowazek* called Chlamydozoa, and if the alga used by *Dunbar* in his experiments was acid-fast, it is no wonder that all bacteria which developed in his cultures proved to be at first also acid-resistant.

It remains to be hoped that some staining reaction will be found later which would allow a differentiation between bacterial gonidia and cell granules, but in view of the ever-changing

composition of both kinds of these smallest units not very great expectations seem to be warranted. Therefore, the heterogenetic hypothesis can not be defeated definitely from this new point of vantage; that it has lost, however, practically all of its probability, is hardly to be disputed. Besides this, the results discussed above are of great practical interest, insofar as valuable suggestions offer themselves for a successful attack of the otherwise extremely difficult problem to secure a speedy upgrowth of normal bacterial cells from their gonidia, which on the commonly used substrates is often out of the question.

2. REPRODUCTIVE ORGANS IN THE DIFFERENT GROUPS OF BACTERIA.

The summary of what is known at present concerning the occurrence of the different types of reproductive organs among the various kinds of bacteria, which is to be given on the following pages for ready reference, will be arranged, on account of the reasons mentioned on p. 6, in the same manner as the review given in the second part of Chapter I along the old familiar lines of grouping. It is, of course, somewhat absurd to write, e. g., upon the spore formation of nonspore-forming bacteria, but we will have to tolerate temporarily such, it is to be hoped, not misleading "absurdities," because a new, more correct classification of the bacteria can not be attempted successfully, before many more results will have been gathered, than are available at the present time.

(a) COCCI.

The formation of minute and of comparatively large forms of micrococci, probably their gonidia and microcysts, were apparently first noticed by *Lübbert* (1886) in the course of his studies upon *Staphylococcus pyogenes aureus*. *Prove* (1887) recorded with his *Micrococcus ochroleucus* normal cells of 0.5–0.8μ, minute coccoid bodies of 0.1–0.3μ, and large forms of 1.6–1.8μ diameters; the latter were called "Dauersporen" on account of their considerable resistance against heat (30 minutes at 100° C.), but they have been evidently microcysts. *Prazmowski* (1888 *a*) found resistant forms regularly with *Micr. ureae*, which survived when exposed for 1 minute to 90° C., but were killed at 100° C. The whole cell was transformed, and no membrane was thrown off during germination. Nevertheless the author insisted that these were "endogenous" spores. Like this, so also the statement made by *DeToni* and *Trevisan* (1889, p. 1072) can not be accepted as referring to genuine endospores, although it reads: endosporae microsomae in coccis normalibus obvenientes.

Irregular rod-like regenerative bodies were observed by *Matzuschita* (1900) when he grew *Micr. flavus liquefaciens* and *M. rubefaciens* on salt agar (see figs. 5 and 6 on Plate I), while other micrococci, including *M. candicans*, did not react in the same manner. The last-named organism, however, gave analogous results when studied by *Löhnis* and *Smith* (1916 *a* and *b*); besides the formation of regenerative bodies the production of gonidia and of microcysts has been discussed in these papers. Some photographs were reproduced as figures 2–4 and 8 on Plate I and 168–169 on Plate XII. The "protospores" found by *Fedorowitsch* (1902) with micrococci as with other bacteria leave no doubt about their being gonidia. Such "exogenous globules" were also seen by *Almquist* (1917) with *Micr. pyogenes*, while his "macrococci" of *Micr. Thulini* furnish another example of microcyst formation.

The important rôle played by the gonidia in the life cycle of the Gonococcus was discovered by *Wertheim* (1899) and more thoroughly studied by *Herzog* (1910–1913), who also secured analogous results with Meningococcus. The latter have been confirmed and considerably extended by *Hort* and his collaborators (1915–1917), whose observations relating to the development of gonidangia, which were mistaken for "asci," are of special importance.

Some data concerning the formation of gonidia, regenerative bodies, and of microcysts by *Sarcina flava* and *Planosarcina ureae* have been secured by *Löhnis* and *Smith* (1916 *a* and *b*). The production of regular endospores by the last-named organism, first described by *Beijerinck* (1901 *a*), together with other morphological data exhibited in the course of its life cycle, points to certain relations with spore-forming bacilli, a fact which was already indicated in an earlier note by *Olsen* (1897).

That the "Dauersporen" seen by *Salomonsen* (1876) in blood cultures of streptococci, have been microcysts, is hardly to be doubted, and this is beyond question in regard to the "spores" or "kystes" of *Leuconostoc mesenterioides*, according to the description given by *Van Tieghem* (1879 *c* and 1884, p. 1108). The same holds true concerning the "arthrosporae macrosomae in filamentis huc illuc sparsae," which were mentioned by *De Toni* and *Trevisan* (1889, p. 1054) as characteristic of the genus Streptococcus. The drawings of streptococci made by *Babes* (1895), which were reproduced as figure 3 on Plate B, those of *Leuconostoc hominis* of *Hlava* (1902), reproduced as figure 4 on Plate B, as well as that of *Streptococcus pyogenes*, made by *Hewlett* (1902) and reproduced as figure 72 on Plate P, are of great interest on account of the details contained therein in regard to gonidia, gonidangia, regenerative bodies, and microcyst formation. All these various types of reproductive organs were also found by *Thiercelin* (1899–1903), when he studied his Enterococcus. His observations upon its gonidia ("microblastes") and gonidangia deserve our special attention, and have been quoted, therefore, more fully on pages 104 and 126. Formation and behavior of these "microblasts" have been thoroughly investigated by *Thiercelin* and *Jouhaud* (1903 *a* and *b*). The peculiar splitting up of microcysts into 3 or 4 parts was first described by *Babes* (1908), and some data upon their resistance against heating (live steam for more than 20 minutes) were obtained by *Holman* (1914). The avirulent, resistant, Micrococcus-like subculture, grown by *Eyre* and *Washburn* (1897) from typical pneumococci, has been evidently a pure culture of regenerative bodies, such as have been photographed by *Axelrad* (1903) from a contact preparate of *Streptococcus lanceolatus*, reproduced as figure 146 on Plate XI.

The important rôle played by filterable gonidia of streptococci as filterable virus in diseases like poliomyelitis, was discussed on the foregoing pages (pp. 145–146).

A good description of gonidangia produced by *Streptococcus lactis* has been furnished by *Maddox* (1885). The spore-like terminal bodies seen by *Weigmann* (1899) at rod-like forms of this species, are probably to be classed as regenerative bodies. Our own experiments with lactic acid streptococci proved once more the regular occurrence of gonidia, regenerative bodies and microcysts. Photographs have been reproduced as figures 11 on Plate I and 170 on Plate XII.

(*b*) NONSPORE-FORMING RODS.

The report and pictures given by *Hauser* (1885) in his Proteus monograph, of what he calls the involution forms of this organism, are mostly to be interpreted as relating to the formation of gonidangia and to the occasional transformation of their content into one rudimentary endospore. A characteristic photograph has been reproduced as figure 120 on Plate X. *Bac. piscicidus agilis* was found by *N. Sieber* (1895) to produce genuine endospores, though it exhibited in all other respects the character of the Proteus group. With *B. Zopfii*, whose arthrospore formation has been studied by *Kurth* (1883), analogous results concerning typical endospore formation were recorded by *Swellengrebel* (1904).

The large globules produced by *B. bifidus* are to be interpreted, according to the description given by *Tissier* (1900), as either gonidangia or regenerative bodies. It was stated in that paper (p. 90):

> De ces boules partent en rayonnant des corps bacillaires d'une grande finesse qui se subdivisent.

The fairly high resistance (80° C. for 1 hour) shown by the Boas-Oppler bacillus, when tested by *C. Sternberg* (1898), which was believed by this author to be due to the presence of spores, may just as well have been the result of the formation of regenerative bodies. The observations of *Sandberg* (1904) and of *Rodella* (1908) are in accordance with this assumption. Some data furnished by the last-named author indicate that also the liberation of gonidia was noticed by him in some cases. *Fokker* (1901), however, seems to have had, indeed, some really endospore-forming lactobacilli. As far as can be seen from his report, his results agree closely with those secured by *Noguchi* (1910), who succeeded for the first time to change experimentally the anaerobic *Bac. bifidus* into an aerobic spore-forming bacillus, resembling *B. mesentericus fuscus*.

The very conspicuous regenerative bodies of lactobacilli have been mentioned by *Weigmann, Gruber,* and *Huss* (1907), *Kuntze* (1908), *White* and *Avery* (1909), *Rubinsky* (1910), *Löhnis* and *Smith* (1916 *a* and *b*), and by others. Figures 148 on Plate XI and 172 on Plate XII demonstrate their characteristic appearance; in the center of the last-named picture a germinating regenerative body is visible. Part or all of what has been described as "granule" formation by *Luerssen* and *Kühn* (1908), *White* and *Avery* (1909) and by *Koegel* (1914), is undoubtedly to be explained as relating to the production of gonidia. As this is quite general, but at the same time naturally varying to some extent, presence or absence of the "granules" can not be made the basis for separating several types or species of lactobacilli, as was done by the first-named authors. *Kuntze's* experiments have already demonstrated the instability of this feature.

The picture of a pure culture of regenerative bodies of *B. cholerae gallinarum*, which was made by *Itzerott* and *Niemann* (1895), who were obviously not aware of the special character of these dark round cells, was reproduced as figure 30 on Plate III. The gonidia of this species, as well as of *B. septicaemiae murium*, have been studied by *Fedorowitsch* (1902) under the name of protospores.

Gonidia, gonidangia, regenerative bodies, and perhaps microcysts, too, may have been seen by *Albrecht* and *Ghon* (1900), when they made the drawings of *B. pestis*, which have been reproduced as figure 11 on Plate D. The important rôle played by the gonidia in the reproduction of this species was pointed out by *N. K. Schultz* (1901). Analogous results with *B. pseudo-tuberculosis rodentium* have been recorded by *Zlatogoroff* (1904). *Maassen* (1904) made an interesting photograph of what he calls teratologic growth of *B. pestis*, reproduced as figure 118 on Plate X as a very suggestive object for comparison with *Hauser's* Proteus picture (fig. 120).

The formation of the typical round lateral regenerative bodies of *B. pneumoniae* has been shown in figure 171 on Plate XII, which was reproduced from our second preliminary paper (*Löhnis* and *Smith* 1916 *b*). Gonidia, regenerative bodies and gonidangia of another member of the *B. pneumoniae* group, the so-called *Proteus hominis capsulatus*, have been fairly well studied by *Bordoni-Uffreduzzi* (1888 *b*). Two interesting drawings of his have been given as figure 14 on Plate D and figure 123 on Plate X; the latter, made from a liver cut, is especially instructive. The production of terminal exospores by *B. acidi lactici* has been ascertained by *Hueppe* (1884) in his first investigations upon the microbial alterations of the milk by microscopic tests as well as by boiling. Though some years later, with *Hueppe's* consent, *Epstein* (1900) has revoked these findings, it still remains probable that they have been correct (cf. p. 137). The photograph of *B. aerogenes* made by *Maassen* (1904), reproduced as figure 119 on Plate X, equally indicates the possibility of inducing this like other "nonspore-forming" bacilli to produce exo- and endospores. *Kitt's* drawing of *B. phlegmasiae uberis*, a variety of *B. aerogenes*, is another good example of the mode of producing regenerative bodies within this group. (See fig. 145 on Plate XI.) That an old stock culture of *Actinobacter polymorphus Duclaux* presented itself to *Lehmann* and *Neumann* (1912, p. 206) as closely resembling *Sarcina tetragena*, would also have to be explained as another case of a pure growth of round regenerative bodies, provided that no error in making the transfers has occasionally happened (cf. also p. 49).

The participation of gonidia and regenerative bodies in the life cycle of *B. coli* has been studied by *Almquist* (1893), *Adami, Abbott* and *Nicholson* (1899) *M. E. Abbott* (1900), *Fedorowitsch* (1902), *Ohlmacher* (1902), and more recently by *Kellerman* and *Scales* (1916), whose very interesting photographs have been reproduced as figures 182, 185, 199, and 200 on Plate XV. The drawing made by *Hort* (1917 *a*) of all forms which he saw in his Coli cultures, reproduced as figure 180 on Plate XIII, deserves also to be examined carefully. Terminal spore-formation of the type seen by *Hueppe* with his *B. acidi lactici*, has been recorded for *B. coli*, though only in one case, by *Piccoli* (1896). The very close similarity of *Maassen's* (1899) *B. esterificans*, which, however, despite its otherwise coli-like character, showed a more pronounced tendency to develop such polar spores, is noteworthy in this connection. What

Rogers, *Clark*, and *Davis* (1914), as well as *Burton* and *Rettger* (1917), have classified as sporogenous members of the Colon-Aerogenes group may have been analogous strains; but it must be left in doubt whether the definition of this group almost entirely by biochemical features, as given by these authors, has not led to an essential alteration in the meaning of the name of the group. The picture made by *Matzuschita* (1900) of large "involution" forms of *B. coli*, reproduced as figure 36 on Plate III, apparently demonstrates a type of gonidangia formation. Another strain was reported to have furnished large globules. Transformation of the inflated parts of threads into large round bodies was actually observed by *Wilson* (1907).

The "small sporoid bodies" found by *Eberth* (1880) in *B. typhi*, 1 to 3 to the rod, have been undoubtedly gonidia; while the round terminal unstainable bodies, described by *Gaffky* (1884) as the spores of this species, seem to belong into the same class as the similar formations found in a few cases with *B. coli* and *B. acidi lactici*. Unstainable spaces within the rods, which have been considered for sometime by *Klebs* (1887, p. 174) and others to be spores, are to be explained with great probability as vacuoles. The negative findings of *Buchner* (1888) and of *Pfuhl* (1888) in regard to typhoid "spores" confirm this view, but, despite a widespread opinion, they can not be accepted as full proof that the terminal bodies seen by *Gaffky* were not spores. This point remains to be settled by future investigations. *Almquist's* (1893–1917) studies, which were mostly centered on this species, have brought out many interesting details concerning formation and further development of gonidia and regenerative bodies by *B. typhosus*. Some of his photographs were reproduced as figures 135, 136, and 138 on Plate XI. Large globular gonidangia, which are mentioned in one of his latest papers (1916), have been described before by *Gamaleia* (1900). Direct microscopical investigations upon the reproduction of normal rods from so-called protospores, i. e., from gonidia, have been made by *Fedorowitsch* (1902). The drawings published by *Hort* (1917 *a*) and reproduced as figure 179 on Plate XIII, furnish a comprehensive picture of probably all forms which may occur in the course of the development of the gonidia and regenerative bodies of the typhoid organism.

Analogous results as with *B. typhosus* have been recorded by *Almquist* (1908–1917), as well as by *Hort* (1917*a*), in regard to paratyphoid and dysentery bacilli, and by *Meirowsky* (1914 *b*) with *B. paratyphosus B.* and *B. enteritidis*. *Meirowsky's* drawings of the paratyphoid organism, reproduced as figure 178 on Plate XIII, make an excellent counterpart to *Hort's* composite pictures of *B. coli* and *B. typhosus*.

Radiate growth, shown in *Hort's* pictures as result of the upgrowth from the gonidial stage, has been found by *Beijerinck* and *van Delden* (1902) to be especially frequent with *B. radiobacter*, which like *B. radicicola* is closely related to the Colon-Aerogenes (*B. pneumoniae*) group. Our own experiments have furnished many confirmative results (*Löhnis* 1905 *a*, *L.* and *Smith*, 1916, *a* and *b*). However, not all radiate growth of bacteria is of the same origin. Sometimes a similar development starts from the symplastic stage, in other cases a stellate arrangement of adult cells is noticeable at the time of conjunction (see Chaps. III and IV). The small "swarming bodies" (gonidia) of *B. radicicola* are known as long as the species itself (*Beijerinck*, 1888). *Frank* (1890), *Prazmowski* (1890), *Morck* (1891), and *Atkinson* (1893) soon confirmed and extended the findings of the Dutch bacteriologist. Some characteristic drawings made by *Morck* were reproduced as figures 66 and 67 on Plate P; they illustrate clearly the formation of the gonidia in the rods, as well as in the gonidangia. The following description given by *Greig-Smith* (1900) concerning the liberation of a budding gonidium of *B. radicicola*, pictures in an excellent manner how this occurrence looks under the microscope not only in this case, but always when motile gonidia are making their way to liberty:

> When the bud has separated from the parent protoplasm it pulls and tugs in its endeavor to free itself from the capsule membrane containing the motionless mother cell, and we have an appearance exactly like that of an ant attempting to drag along a twig which proves too heavy for its powers.

"Zoospores" (gonidia) growing up to new rods within a "mother spore" (gonidangium) have been seen by *Hartleb* (1900). What *Hiltner* (1900) called spores may have been gonidia as well as regenerative bodies, and the so-called sporangia of *B. radicicola* (*Hiltner* and *Störmer*, 1903, pp. 210, 262) are to be interpreted either as gonidangia or as large irregular regenerative

bodies, produced by the symplasm, a type of the so-called bacteroids, which readily break up into round regenerative bodies. Photographs were reproduced as figures 195 and 196 on Plate XV, and more data relating to this type of regenerative bodies are to be found in the papers of *Rossi* (1907), *Peklo* (1910), and *Spratt* (1912). An exceptionally high resistance of such bodies against heating has been reported by the last-named author.

The big inflations of acetic acid bacteria, which were studied by *E. Chr. Hansen* (1879, 1894, see fig. 15 on Plate E), are typical gonidangia. Gonidia and microcysts have been also seen by the Danish author, and excellent drawings of regenerative bodies, published by *Henneberg* (1898) were reproduced as figure 57 on Plate N.

Some white and yellow short rods, found by *A. Wolff* (1908) in milk, furnish another interesting example of a comparatively high resistance of regenerative bodies against heating. At least part of the round forms withstood boiling for 15 minutes. Large pear- or bottle-shaped cells, probably gonidangia, were also observed in the cultures.

That the yellow or red pigmented spore-forming bacillus isolated by *Morgenthaler* (1916) is to be considered to represent probably a sporogenous variety of *Bact. herbicola,* and that *B. violarius acetonicus* of *Bréaudat* (1906) appears to be the analogous counterpart to *Bact. violaceum,* has been pointed out on page 137.

Gonidia, gonidangia, and regenerative bodies of *B. cyanogenes* have been correctly described by *Neelsen* in 1880. But what he called the spores of this species have been evidently mostly, if not all, vacuoles. Genuine exospores, however, have been found by *Hueppe* (1884).

The very interesting fact that gonidia and regenerative bodies of *B. fluorescens* have been photographed by *R. Koch* as early as in 1877, though later overlooked entirely, has been mentioned on page 92. Only one year later *Ewart* (1878 *a*) published another but more complete description of the same occurrence. One of our own photographs (*Löhnis* and *Smith,* 1916 *a,* fig. 40) has been reproduced as figure 110 on Plate X as counterpart to the picture made by *R. Koch* 40 years earlier, reproduced as figure 109. Another characteristic illustration of the next step in the development of what *Koch* called lateral spores was shown as figure 174 on Plate XII (*Löhnis* and *Smith,* 1916 *b,* fig. 28). Genuine spore formation by some Fluorescens strains has been recorded by *Tanner* (1918). *Bact. bruneum,* of which *Matzuschita* (1900) obtained a pure culture of globular regenerative bodies (see fig. 18 on Pl. II) may be also mentioned here, because it is hardly to be doubted, that it is to be classed as one of the brown varieties which are rather common in the Fluorescens group. Special studies upon gonidia, gonidangia, and regenerative bodies of *B. fluorescens* and of another organism with polar flagella (*Pseudomomas cerevisiae*) have been made by *Fuhrmann* (1906–1908).

That Nitrosomonas as well as Nitrobacter are endowed with the same types of reproductive organs is fairly well indicated by the photographs made by *Winogradsky* (1891–1892), reproduced as figures 49–53 on Plate V. And it is very probable, as was pointed out on page 135, that *Winogradsky's* Nitrosococcus is no separate species, but a pure culture of regenerative bodies of Nitrosomonas.

(*c*) SPORE-FORMING RODS.

That *B. anthracis* is accompanied within the tissue by its gonidia and regenerative bodies has been demonstrated by *R. Koch* (1877) in the first photograph which he made of this organism (reproduced as fig. 111 on Pl. X); though no explanation was given by him in regard to the round bodies visible therein. It was left, therefore, to *Ewart* (1878 *b*) to give the first detailed description of the mode of formation and development of these reproductive organs. Although he speaks of spores, it is quite evident from his general report, as well as from the fact that these bodies did not withstand boiling, that the term was used in a different manner as is customary to-day. Soon afterwards *Fokker* (1881) strongly emphasized the important rôle played by these coccoid reproductive organs, especially in the beginning of the disease, which had been overlooked by *R. Koch,* though they were once more photographed by him (*Koch,* 1881) in the picture reproduced as figure 113 on Plate X. *Archangelski* (1883), *Roloff* (1883), and *E. Klein* (1883) soon furnished more confirmative material in this direction; pure cultures of the round bodies were grown by the first-named author through three successive transfers

and then reverted promptly to normal rods. Equally early discoveries made by *Toussaint* upon the formation of gonidangia by *B. anthracis,* and upon the liberation and further development of the gonidia produced therein, have been reported in the textbook of *Magnin* and *Sternberg* (1884, p. 150). Similar findings were made by *Weibel* (1888) and by *Schroen* (1890). The possibility of an occasional replacing of the regular endospores by gonidangia has become very clear by these contributions. A curious, but highly characteristic statement, by which *Fraenkel* (1891) tried to discard gonidia and regenerative bodies of *B. anthracis* as "unnecessary" and "illegitimate," because they "merely" reproduce the "legitimate" rods, has been quoted on page 27. *Rodet* (1894, p. 18) confirmed once more the correctness of *Toussaint's* observations and the results obtained by *Chauveau* and *Phisalix* (1895) with an Anthrax strain of low virulence, in which the endospore formation was entirely and constantly replaced by the production of round terminal regenerative bodies, represents another important contribution to our knowledge of the physiological value of these reproductive organs. The photograph made by *Matzuschita* (1900) of *B. anthracis* grown on salt agar, reproduced as figure 57 on Plate V, shows also regenerative bodies mixed with endospores. And the photograph published by *Günther* (1906), which was reproduced as figure 112 on Plate X, makes a very interesting counterpart to the two Anthrax pictures of *R. Koch* (figs. 111 and 113). *Růžička* (1908) came again very close to the results secured by *Ewart, Toussaint,* and others of the earlier workers, whose publications evidently had remained unknown to him. *M. Müller* (1912) thinks that asporogenous strains of *B. anthracis* occur much more frequently in nature than is generally assumed; and *McFarland* (1916, p. 359) gives in his textbook an interesting picture of "Anthrax bacilli in glomeruli of kidney" showing many small round bodies close to and stained like the bacilli, which is very similar to *Koch's* early photographs. *Henri's* important paper (1914) upon the transformation of regular Anthrax bacilli into round (regenerative) bodies and into an asporogenous Actinomyces-like growth has been quoted repeatedly. The most characteristic photographs contained therein were reproduced as figures 58–63 on Plates V and VI.

A good picture of a lateral regenerative body of *B. subtilis* has been published without comment by *Hiss* and *Zinsser* (1914); it was reproduced as figure 150 on Plate XI. Other photographs showing gonidia and regenerative bodies as formed by this organism have been furnished in our preliminary papers (*Löhnis* and *Smith,* 1916 *a* and *b*); two of them were reproduced as figures 65 on Plate VI and 197 on Plate XV.

The big globules found by *Blau* (1905, p. 125) in cultures of his *B. cylindricus,* which either contained several small plasmatic globules or one endospore, evidently have been gonidangia, while other round cells, seen by *A. Meyer* (1901) in cultures of *B. cohaerens, Ellenbachensis* and *ruminatus,* have been typical microcysts. Two drawings made by the last-named author have been reproduced as figure 64 on Plate O.

A spore-forming aroma producing bacillus, isolated by *Burri* (1897) from Swiss cheese, exhibited quite constantly with all six strains studied "granular differentiation" of the plasma, coiling of the granular rods into ring forms and development of large globules of several micra diameter, which appeared like a conglomerate of small cocci. In the textbook of *Lehmann* and *Neumann* (1912, p 460), wherein the bacillus was named *B. bernensis,* no indication whatever is given concerning this interesting report of the Swiss author in regard to the formation of gonidia and gonidangia by this species.

The large globular forms of *B. Megaterium,* described by *DeBary* (1884, p. 503), may have been either gonidangia or microcysts, while the "Bacillen-Säckchen," found by *Schroen* (1890) with this species, as well as with *B. anthracis,* leave no doubt as to their having been gonidangia. The same holds true with regard to similar cells of *B. Ellenbachensis* observed by *Stoklasa* (1898, p. 120).

Regular endospore formation was recorded by *Zopf* (1883) with the rod-like, but also with the large globular cells of *B. tumescens.*

Bac. oxalaticus was found by *Kuntze* (1904) to produce abundantly "swarming bodies" (gonidia). Their liberation was seen, but not their further development.

That the large round cells of Azotobacter are a type of growth of endospore-forming bacilli became evident from the behavior of some of our old stock cultures (*Löhnis* and *Hanzawa*, 1914). Investigations made by *Ford* (1916) upon numerous sporogenous bacilli have shown, on the other hand, that many, if not all of them, are able to produce cells looking very much like Azotobacter. What *Beijerinck* (1901) called involution forms of this species have been probably gonidangia, as was pointed out on page 126 when discussing *Beijerinck's* photograph of these cells, reproduced as figure 189 on Plate XV. The very characteristic microcysts of *B. Azotobacter* have been described as "spores" by *H. Fischer* (1905), *Krzemieniewski* (1908), and *Prazmowski* (1912). The last-named author's extended investigations upon this species have added much valuable material to our knowledge of the production and development of the gonidia and gonidangia of Azotobacter. Some of our own photographs of the different types of reproductive organs, as found with this organism, have been reproduced as figures 19–21 on Plate II, 68–70 on Plate VI, 186–188, 190, 191, and 193 on Plate XV.

Good development of lateral regenerative bodies was shown by a bacillus isolated from "Hackfleisch" (chopped meat), when it was grown by *Maassen* (1904) on lithium chloride agar; a photograph of it was reproduced as figure 149 on Plate XI. A not yet completely studied yellow bacillus, No. 41 of our collection, apparently related to *Maassen's* organism, exhibits very prominently the formation and development of gonidia and regenerative bodies, as is illustrated by the photograph reproduced as figure 183 on Plate XV.

An interesting description of the upgrowth of *B. Amylobacter* from what seems to have been its gonidial stage has been given more than 50 years ago by *Trécul* (1867 *b*). *Winogradsky* (1902), on the other hand, noticed the production of small coccoid bodies by his *Clostridium Pastorianum*, but he was of the opinion that they were unable to act as reproductive organs. Asporogenous strains, developed from this species, were morphologically, as well as physiologically, so different from the original culture, that they were hardly recognizable as such.

The "cocco-gonidia" of *B. Chauvoei* have been studied by *Ehlers* in 1884. In the animal they grew up to typical rods. The photographs published by *Grassberger* (1903), *Grassberger* and *Schattenfroh* (1907), and by *Hibler* (1908), some of which were reproduced as figures 74–77 on Plate VII, 115 and 116 on Plate X, and 151 on Plate XI, contain many interesting details concerning gonidia, gonidangia, and regenerative bodies, though they have been grossly misunderstood, especially by the last-named author, as was discussed on pages 67 and 95.

That according to *Hibler's* observations old weakened cultures of *B. Chauvoei* are inclined to produce polar spores, is of special interest when brought into parallel with the so-called involution forms of this species, as photographed by *Fraenkel* and *Pfeiffer* (1895, reproduced as fig. 117 on Plate X) and also with the fact found out by *Grassberger* and *Schattenfroh* (1907), that temporarily asporogenous anaerobic butyric acid bacilli, when returning to spore formation, at first pass through a stage where they exhibit the appearance of a typical plectridium.

(*d*) SPIRILLA AND SPIROCHAETS.

The various reproductive organs of *V. cholerae* (gonidia, gonidangia, and regenerative bodies) have been seen apparently for the first time by *Ferrán* (1885), but the various unfounded hypotheses which he liberally added to his observations, have been evidently the cause that the latter did not meet with adequate interest, though they were confirmed, at least in part, by *Ermengem* (1885, pp. 334–342). The results secured by *Dowdeswell* (1889–1890) and by *Schroen* (1890) are in complete agreement with those of *Ferrán*, but they, too, despite their being all based on direct continuous microscopic examinations, have not been acknowledged by the then dominating German bacteriologists. Even the careful and undoubtedly very correct studies of *Hueppe* (1885) upon the formation and germination of the terminal round regenerative bodies (or exospores ?), which he called arthrospores, were not "officially" accepted Because *Kitasato* (1889) was not able to observe germination of the granules resulting from the "granular decomposition" of the cholera bacilli in old cultures, *Hueppe's* quite different positive findings were declared by *Woodhead* (1891, p. 168) and by *Pfeiffer* (1896, p. 536) to be entirely erroneous, though also *Babes* (1889) reported to have obtained the same results as *Hueppe*.

A good photograph of cholera regenerative bodies, reproduced as figure 140 on Plate XI, has been published by *Friedrich* (1892); but no word of explanation was given by him in regard to the round bodies clearly visible in the picture. Upgrowth of new vibrios from the gonidia has been recorded by *Cantacuzène* (1898), *Bliesener* (1901), *Kohlbrugge* (1901), and *Fedorowitsch* (1902), while the germinating globules seen by *Nakanishi* (1901) have been apparently regenerative bodies. The large globules visible in the photograph made by *Maassen* (1904), which was reproduced as figure 121 on Plate X, are gonidangia wherein spore-like bodies have replaced the normal gonidia. Thorough studies upon formation, multiplication, and germination of the round regenerative bodies of *V. cholerae* have been contributed by *Almquist* (1904–1917); they confirm once more the accuracy of *Hueppe's* early work, and the photograph reproduced as figure 139 on Plate XI deserves to be studied jointly with figure 49 on Plate M. A photograph of a pure growth of the round reproductive organs of the cholera organism made by *Hammerl* (1906) has been reproduced as figure 158 on Plate XII. Many data given in the more recent publications of *Bittrolff* (1912) and of *Stamm* (1914) are in full agreement with the early findings of *Ferrán*, *Dowdeswell*, and *Schroen*.

Very similar results have been recorded by *Finkler* and *Prior* (1884–1885) with the vibrio isolated by them from cases of cholera nostras. The formation of gonidia, gonidangia, and of regenerative bodies has been fairly well studied. Germination of the round regenerative bodies of this species, as well as of *V. Metchnikovii*, was also observed by *Nakanishi* (1901). That the spores attributed by *Gamaleia* (1888) to the last-named organism have been such indeed may be justly doubted; the staining reaction, upon which this opinion was based, is certainly not so conclusive as was generally assumed at that time. Evidently the same holds true in regard to the "spores" or "sporelike bodies" found by *Van Tieghem* (1879 *b*), *Weibel* (1888), *Hueppe* (1891), and others with various vibrios. They all have been mistaken gonidia, regenerative bodies or vacuoles. With a *Vibrio proteus*, isolated by *Kohlbrugge* (1900) from water, the reproduction of normal cells by gonidia and regenerative bodies has also been ascertained.

Germination of the so-called spores of *Spirillum amyliferum* has been recorded by *Van Tieghem* (1879 *a*). How the sprouting of the gonidia may lead to a characteristic branching of the parent cells has been shown by *Sorokin* (1887–1890). Some drawings of his *Spirillum endoparagogicum* were reproduced as figure 29 on Plate H. That the term "spores" was incorrectly applied in this case by the author is proven by his statements that these "spores" had no distinct membrane and were not more resistant against heating than the vegetative cells. The analogous round bodies found by *Esmarch* (1887) within *Spirillum rubrum* leave also hardly any doubt that they are to be classed as gonidia. As *Meirowsky* (1914 *b*) has demonstrated, they may grow up in exactly the same manner as those of *Sorokin's* spirillum. A sketch illustrating this fact was reproduced as figure 30 on Plate H; Plate XIV offers further information. Interesting data upon the regenerative bodies of this species, as well as of *Spirillum tyrogenum*, have been also collected by *Meirowsky*. Figure 167 on Plate XII and the lower part of Plate XIV may be compared in this respect. Branched forms like those described by *Sorokin* and *Meirowsky* have been seen by *Kutscher* (1895) with *Spirillum Undula* and *Sp. Serpens*. But neither he nor *Zettnow* (1896) reached a correct insight into the real character of the round bodies within the spiral cells, which are the cause of this branching. Photographs made by *Doerr* (1905) of *Spirillum pyogenes* show some other case of branching and budding; they, too, were published, however, without any explanatory remark in the text. Two salt-water spirilla furnished us (*Löhnis* and *Smith* 1916 *a*) very good examples of the mode of branching first seen by *Sorokin*. Formation and germination of the round terminal regenerative bodies were equally conspicuous.

The ability of certain spirochaets to produce arthrospores has been discovered by *Van Tieghem* (1879 *b*) in regard to an oyster parasite, and by *Zopf* (1881) with *Spirochaeta plicatilis*. Their findings have been recently confirmed by *Gross* (1912–1913), whose drawings were reproduced as figure 63 on Plate O, and by *W. H. Hoffmann* (1912).

The first information upon the occurrence of motile gonidia with *Spirochaeta Obermeieri* and their participation in the life history of this species has been furnished by *Heydenreich*,

Guttmann (1880), and *Albrecht* (1881). In regard to *Spirochaeta pallida* analogous results have been secured by *Wechselmann* and *Löwenthal* (1905), *Leuriaux* and *Geets* (1906), *McDonagh* (1912–1913), and *Meirowsky* (1914). Data concerning the round terminal and lateral regenerative bodies of this species were also published by the last-named author, as well as by *Mühlens* (1907), by *Krzysztalowicz* and *Siedliecki* (1908), and by *Selenew* (1910). Similar facts have been recorded with various other spirochaets by *Krienitz* (1906), *Mühlens* and *Hartmann* (1906), *Gonder* (1909), and especially by *Noguchi* (1911–1912) with all his pure cultures of different spirochaets (*Sp. pallida, micro-* and *macrodentium, mucosa, Duttoni, phagedenis* and *gallinarum*). Gonidia, as well as regenerative bodies, were also observed by *Calmette* (1893) with the spirochaetelike organism, discovered by him in cases of typhus exanthematicus, by *Bonhoff* (1905) with his *Spirochaeta vaccinae*, by *Breinl* (1905) and *Leishman* (1918) with *Spirochaeta Duttoni*, by *Fantham* (1911) with different species, *by Hindle* (1911) with *Spirochaeta gallinarum*, by *Bosanquet* (1911) with *Spirochaeta anodontae*, by *Tunnicliff* (1913) with a spirochaete associated with infections of the accessory sinuses, and by *Inada* and his collaborators (1916) with *Spirochaeta icterohaemorrhagica*. The rôle played by the "infective granules," and their ability to reproduce the spirochaets has been further discussed by *Leishman* (1909–1918), *Balfour* (1911–1913), *Rüther* (1910), and by *King, Baeslack* and *Hoffmann* (1913).

The formation of microcysts by spirochaets has been studied by *Breinl* (1907), *Dutton* and *Todd* (1907), *Doflein* (1909), *Gonder* (1909), *Fantham* (1911), and by *Inada* et al. (1916). As the first-named authors found out, the gonida are liberated within the microcyst, which, therefore, acquires the character of a gonidangium.

The motile gonidia of fusiform bacilli have been discovered by *Plaut* (1907) and their regenerative bodies by *Ellermann* (1907) who, however, thought they were to be classed as involution forms. *Rosenow* and *Tunnicliff* (1912) observed the slipping out of the gonidia from the bacilli, whose ends may become inflated, assuming the character of gonidangia. Multiplication of the "cocci" as such was also seen.

(*c*) MYCO- AND TRICHOBACTERIA.

With *B. tuberculosis* gonidia, gonidangia, and regenerative bodies have been seen undoubtedly, whereas concerning arthrospores and microcysts no such definite statement can be made, though it is probable that they, too, have been observed. The 2–6 unstainable "spores," attributed by *R. Koch* (1882–1884) to his bacillus, have been either vacuoles or gonidia. Motile gonidia ("Schwärmsporen") were discovered by *Klebs* (1883 *a*). Similar "grains bien colorés" have been mentioned by *Babes* (1883), but in addition swellings of the bacilli "suivant leur longeur" were registered, which may have been growing gonidangia. The occurrence of these reproductive organs with tubercle bacilli has been ascertained by *Schroen* (1886–1904). The description given by *Lutz* (1886) of the coccoid bodies within the bacilli, and of the large round deeply staining or not stainable thick-walled bodies at the end of the rods, leaves no doubt upon their being gonidia and regenerative bodies or exospores, respectively. *Metchnikoff* (1888 *a*) observed that oval cells broke off from short side branches, but whether these should be classified as arthrospores or as regenerative bodies, can not be decided at present. His drawings, reproduced as figure 38 on Plate J, do not permit a final conclusion. Some of the large swellings shown look very much like gonidangia. Slipping out of the gonidia was seen by *Mafucci* (1892). The occurrence of unstainable sporoid bodies within terminal swellings of the bacilli has been recorded by *F. Fischel* (1893), while *Sander* (1893, p. 277) studied not only the formation but also the germination of deeply staining, polar regenerative bodies. The exceptionally high resistance, ascribed by *Marpmann* (1893) to "spores" of the tubercle bacilli, which are reported to have not died when kept for 1 hour in the steam, can not be fully explained at present. If not the result of a faulty test, which seems most probable, it may be that either sporelike bodies, such as those seen by *Lutz* and by *Fischel*, have reached an exceptionally high degree of resistance, or comparatively large clumps of symplasm have been present, which have shielded some of the germs enclosed therein. Simultaneous upgrowth of numerous thin threads from clubs (i. e. gonidangia) of the tubercle bacilli has been noticed by *Coppen-*

Jones (1893). *Semmer* (1895) reported that he saw the small globoid bodies reproduce normal bacilli, after they had been liberated by rods and clubs.

A characteristic sketch of regenerative bodies made by *Crookshank* (1896) has been reproduced as figure 55 on Plate N. *Schürmayer* (1898 *a*) met with small motile not acid-fast granules, which either multiplied as such or grew again up to rods. The pictures published by *Arrigo* (1900), which were reproduced as figures 103 and 104 on Plate IX, are very suggestive of arthrospores and microcysts; but as the mode of formation of these bodies is not definitely known, the possibility remains that they, too, have been gonidia and regenerative bodies. Arthrospores ("conidia") produced by "aerial hyphae" of the tubercle organism, were also recorded by *Droba* (1901), besides lateral regenerative bodies, which he called "zygo- and stylospores." Other instances of germinating tubercle gonidia have been mentioned by *Fedorowitsch* (1902) and by *Rosenblat* (1905). In the latter case arthrospores, too, may have been seen; and the so-called "Splitter" of the tubercle bacilli, as found by *Spengler* (1905–1907), apparently have also included both types of reproductive organs. The description which *Betegh* (1908) furnished of them confirms this view. That the "granules" of *Much* (1907) are to be interpreted as gonidia is beyond doubt, and it is equally certain that much of what has been written about this discovery by *Much* (1907–1909), *Wirths* (1908), *Knoll* (1910), *Heinrich* (1912) *Kirchenstein* (1912–1913) and by others, could have well been spared if the earlier observations would have been properly considered. An interesting, but not easily accessible, contribution relating to the tubercle gonidia, whose partial filterability was ascertained in this case, was published by *Fontes* (1910). That the acid-fast as well as the not acid-fast "cocci" produced by the tubercle bacilli may develop as such has been further studied by *Maher* (1910–1913). The large acid-fast coccoid bodies seen by *Wherry* (1913) have been evidently regenerative bodies. Probably the most thorough investigation upon formation and development of gonidia and regenerative bodies of *B. tuberculosis* thus far published has been made by *Meirowsky* (*1914 b*); some of his pictures were reproduced as figures 162–164 on Plate XII and on Plate XIV.

That *B. leprae* is able to develop regenerative bodies has been ascertained by *A. Neisser* (1881) and by *G. A. Hansen* (1882), both of whom called them spores. Gonidia, as well as regenerative bodies and exospores, of this organism have been studied by *Babes* (1883) and more thoroughly by *Lutz* (1886). *Bordoni-Uffreduzzi* (1888 *a*) termed the polar swellings arthrospores. Their germination to bacilli has been probably first seen by *Czaplewski* (1898). The occurrence of sporelike inclusions within what has been either regenerative bodies or gonidangia of the leprosy organism was recorded by *Babes* (1907). Very interesting pictures of the different reproductive organs of *B. leprae*, made by *Kedrowski* (1910), were reproduced as figure 37 on Plate J and as figures 153 and 154 on Plates XI and XII. Others published by *Meirowsky* (1914 *b*) are to be found on Plate XII (figs. 165 and 166) and on Plate XIV.

Liberation and germination of the gonidia produced within the threads and the gonidangia of *B. mallei* have been probably first discussed by *Semmer* (1895) as an analogous occurrence to the same type of reproduction of *B. tuberculosis*. *Marx* (1899) and *Conradi* (1900) saw only lateral development of the gonidia into buds and branches, and reached the conclusion that no spores were formed, because no resistance against heating could be ascertained. *Wladimiroff* (1903), however, pointed out that the granules formed by the rods can preserve the life of the species for a very long time, and he places them parallel to those granules (i. e. gonidia) studied by *N. K. Schultz* (1901) and by *Rothert* (1902) with *B. pestis* and numerous other bacteria. The rather high resistance which, according to *Lehmann* and *Neumann* (1912, p. 548), has been occasionally observed with *B. mallei* by *Bonâme*, who found that a temperature of 70° C. could be endured for 6 hours, and 90–100° C. for 3 minutes, clearly indicates that also in this case regenerative bodies, arthrospores, or microcysts may have exerted their influence. In the photographs made by *Carpano* (1913) of this organism, reproduced as figures 91–96 on Plate VIII, gonidia, gonidangia, and regenerative bodies are well discernible, while in regard to the occurrence of arthrospores and microcysts no definite answer can be secured, neither from the picture nor from the paper itself.

The gonidia of *B. diphtheriae* were considered by *Klebs* (1887) to be spores. According to *Cornil* and *Babes* (1890, Vol. II, p. 59) reproductive organs of comparatively high resistance against boiling water have been found by the latter author in 2 among 42 cases, but their exact nature was not determined. That the gonidia are not spores was emphasized against *Klebs* by *Escherich* (1894, p. 73), who in addition pointed out (p. 83) that the club-shaped cells should not be classed as sign of degeneration, because they develop in abundance on serum within 24 hours. Radiate and parallel growth shown by *B. diphtheriae* was declared by him (l. c., p. 87) to be caused by the germination of the "chromatine granules" to new rods. Good pictures of typical lateral regenerative bodies of this species have been published by *Bernheim* and *Folger* (1896) and by *Spirig* (1903). The last-named author's publications upon this subject (1899, 1903) give also valuable information upon occurrence and germination of gonidia and arthrospores. Liberation and upgrowth of diphtheria gonidia have been further recorded by *Cache* (1901) and by *Fedorowitsch* (1902). *Chester* (1901, p. 14) sees in them the cause of the resistance of diphtheria bacilli against drying; but it is more probable that regenerative bodies and arthrospores also in this case are of greater importance. Pure coccoid growth of diphtheria, observed by *J. Dale* (1910), *Balfour* (1911 *d*), and by *Park* and *Williams* (1914, p. 294), was evidently the result of round regenerative bodies multiplying as such for some time. In secondary colonies normal rods were seen to grow again by the first-named author. Interesting illustrations showing the various reproductive organs of B. diptheria may be found in *Bergstrand's* paper (1918).

What *A. Neisser* (1888) called the endospores of *B. xerosis* was obviously what we now call gonidia. Especially their lateral germinating while still within the rods, together with their moderate resistance against heating, leaves no doubt in this respect. What *Neisser* on the other hand calls gonidia are those clubbed cells to which this name was given by *Bollinger* (1877), when he first saw them with Actinomyces, which, however, when they are fully developed, become either gonidangia or regenerative bodies. The "sporogenous" pseudo-diphtheria bacillus described by *Simoni* (1898) owed its moderate heat resistance (80° C. for 10 minutes) probably to its ability to produce regenerative bodies or arthrospores, such as *Nakanishi* (1900 *c*) found with his diphtheroid *Bac. variabilis*. A characteristic photograph made by the latter author was reproduced as figure 98 on Plate IX. Others published by *E. de Negri* (1916), showing gonidia and regenerative bodies of a Corynebacterium causing malignous granulom, have been reproduced as figures 99 and 101 on Plate IX and as figure 184 on Plate XV. The regenerative bodies were seen to reproduce either normal rods and threads or again budding round forms, as all such regenerative bodies are able to do; the latter, however, were mistaken by the author as being the growth of a Blastomyces.

The description of *Streptobacillus pellagrae* as given by *Tizzoni* and *Angelis* (1913–1915) contains sufficient data from which it may be concluded that gonidia, regenerative bodies, arthrospores, and microcysts have probably all been seen with this Actinomyces-like organism.

The so-called *Streptothrix cuniculi* of *Schmorl* (1891), which is identical with *Bang's* necrosis bacillus, has furnished instructive pictures of gonidia and gonidangia, which have been reproduced as figures 89 and 90 on Plate VIII. Both were found by *W. Ernst* (1902) to be somewhat more resistant than the vegetative cells.

Typical arthrospores, formed especially by segmentation of the aerial hyphae, have been observed quite regularly with probably all Actinomycetes, for instance by *J. Israël* (1878), *Gasperini* (1889), *Domec* (1892), *Garten* (1895), *Kedzior* (1896), *Rullmann* (1896), *Lachner-Sandoval* (1898), *E. Levy* (1902), *Neukirch* (1902), *Doepke* (1902), *Feistmantel* (1902), *Gilbert* (1904), *Schütze* (1908), *Krainsky* (1914), and others. Data referring to the liberation of the gonidia formed within the threads or in the clubs, which act occasionally as gonidangia, are not quite so frequent. They may be found in the papers of *J. Israël* (1878), *Mac Fadyean* (1889), *Bostroem* (1890), *Eppinger* (1890), *Crookshank* (1896, p. 437) and *Loele* (1908). Of special interest is the discovery made by *Hollandt* (1906) that a typical Actinomyces occasionally may develop micro- and macro-gonidia like a Crenothrix, and that these may also germinate within the widened sheath, giving rise to big bundles of new thin threads. While in this case the relationship

to the trichobacteria is very pronounced, connections with the other bacilli, especially with those producing endospores, are indicated by the tendency of some Actinomycetes to develop only one spore at the end of their side branches, as was observed, e. g., by *Schütze* (1908) and *H. U. Williams* (1912). Such "spores" may look very much like the common lateral regenerative bodies, but there is also the possibility that they may consolidate their content to a regular endospore, then showing a growth as was obtained by *Olsen* (1897) with *B. mycoides.* A characteristic sketch was reproduced as figure 20 on Plate F. What *Cozzolino* (1900) described as *Bac. filamentosus,* found in a case of pseudo-actinomycosis, exhibits also very clearly at the same time the morphological and physiological character of an Actinomyces and that of an endospore-forming bacillus. The same holds true in regard to a spore-forming Gram-positive organism, isolated by *Gruner* and *Fraser* (1912), which was said to have been "regarded by others as diphtheroid." *Mycobacillus synovialis,* isolated by *Chantemesse, Matruchot* and *Grimberg* (1917) from a case of arthritis, produced typical endospores which withstood 90° C. for 30 minutes.

Formation, liberation, and development of the gonidia of the trichobacteria are fundamentally the same as in the case of all other bacteria, but the usually much larger size of these reproductive organs made it more easy to find out that they really play an important rôle in the life cycles of these organisms.

The gonidia of Leptothrix have been studied by *Robin* (1853), *Hallier* (1865), *Miller* (1883), *Arustamow* (1889), *Dobrzyniecki* (1897), and *Beust* (1907). But it is hardly necessary to emphasize that not only the material used in these experiments has been by no means pure, the whole "genus" itself is obviously a mixture of large thread-like forms of very different bacteria.

Data relating to the gonidia of Crenothrix are to be found in the publications of *Cohn* (1870), *Zopf* (1879), *Giard* (1882), and *Rullman* (1907). Those of Cladothrix have been described by *Zopf* (1881), *Billet* (1890), and *Ellis* (1912), those of Beggiatoa by *Zopf* (1881–1883), *Engler* (1882), and *Zopf* (1895), and those of Clonothrix and of other iron bacteria by *Schorler* (1904), *Ellis* (1907–1910), and *Petschenko* (1913).

That the other types of bacterial reproductive organs, viz. regenerative bodies, arthrospores, and microcysts, as well as endospores, seem to be entirely absent in this group is probably to be explained by the strictly aquatic mode of life to which all these organisms have adapted themselves. To some extent the macro-gonidia may replace those more resistant bodies and help to preserve the life during dry spells. In addition, the comparatively thick sheaths of the trichobacteria are also enabled to act, in case of need, as protective organs.

3. CONCLUSIONS.

According to the details discussed on pages 90–162 the present status of our knowledge of the various modes and organs of bacterial reproduction can be defined as follows:

(1) Contrary to the monomorphistic theory, which only knows of one constant type of vegetative cell for every species, and of not more than one type of reproductive organ, the endospore, for merely one group of bacteria, it has been ascertained by numerous independent investigations that in reality all bacteria are not only distinctly pleomorphous in their vegetative growth, but are also able to produce various organs of reproduction. These are: Gonidia, regenerative bodies, exo- and endospores, arthrospores, and microcysts. All of them are made up of nuclear substances, which are reinforced by smaller or larger amounts of reserve material and protected by a more or less resistant membrane. Gonidia and regenerative bodies participate actively in the process of multiplication, whereas the other reproductive organs are in the first place resting forms. Gonidia, regenerative bodies, and probably microcysts, too, are produced by all bacteria, while arthrospores, exo- and endospores are less common; though there are indications that they will be discovered in many more cases, as soon as these problems are more thoroughly investigated.

(2) That gonidia play an important rôle in the multiplication and reproduction of bacteria has been discovered by *Perty* in 1852, and as the result of numerous later studies it has become

certain that they are common with all bacteria. Two to four or more gonidia may be produced within every cell; their formation is most abundant when the bacterial development is at its height. They may start growing while still within the parent cell, forming buds and branches or directly new vegetative cells within the old membrane, or they may be liberated either by actively piercing the cell wall or after the membrane has been partially broken or completely dissolved. Sometimes they remain temporarily attached to the parent cell by a comparatively long stem. Most of them, if not all, are enabled to display active motility. One long flagellum has been found as organ of locomotion. Their resistance against heating is not much higher than that exhibited by the vegetative cells, but they are more persistent under unfavorable environmental conditions, especially when exposed to drought. Direct upgrowth of the gonidia to new vegetative cells is not often noticeable in artificial cultures, on account of their minute size, their motility, and lack of suitable nourishment; but it has been observed occasionally with representatives of all groups of bacteria, e. g. with staphylo- and streptococci, Gonococcus, Meningococcus and Enterococcus, with *Bact. pneumoniae*, *typhi*, *coli*, *pestis*, *septicaemiae*, *pyocyaneum*, and *fluorescens*, with *Bac. anthracis*, *Megaterium*, *Azotobacter*, *Amylobacter*, *Chauvoei*, and *oedematis maligni*, with *Vibrio cholerae* and *proteus*, with various spirilla and spirochaetes, *B. fusiformis*, *Corynebacterium diphtheriae* and *mallei*, *Mycobacterium leprae* and *tuberculosis*, Actinomycetes, and with the various trichobacteria. Small clumps of gonidia may give rise to a distinctly star-like growth of bacteria, as it is very common with *B. radiobacter* and *radicicola*. Because of their variable chemical composition gonidia have been frequently mistaken as fat, volutin, or other reserve material. They have been also erroneously discarded as sign of plasmolysis when still enclosed in the parent cell, or as product of "granular decomposition" or of "partial bacteriolysis" after having been liberated by the dissolution of the cell wall. Within the blood and tissue, where they may replace the vegetative bacterial cells more or less completely, they have been confounded with hemoconia, cell granules, and other nonbacterial corpuscles. On and in the generally used cultural substrates they usually multiply as such, producing a very scant growth, which is only noticeable on very careful inspection. The higher resistance of the gonidia against chemical substances, like salvarsan, may become of importance in the medical treatment of chronic diseases.

(3) Not infrequently the bacterial cells increase considerably in size and undergo certain morphological changes before they begin to produce gonidia. This is the case when they become gonidangia, which are able to give birth to a large number of gonidia. The so-called giant forms of spherical, oval, spindle-, pear-, or club-shaped appearance, which usually have been lightly dismissed as "involution forms," have always proved to be gonidangia whenever they have been carefully examined. Formation of gonidangia has been discovered, for instance, with Gonococcus, Meningococcus, Enterococcus, Pneumococcus, *Streptoc. lactis*, *Bact. proteus*, *pestis*, *coli*, *typhi*, *aceti*, *radicola*, *fluorescens* and *cyanogenes*, *Bac. anthracis*, *Megaterium*, *Azotobacter* and *Chauvoei*, *Vibrio cholerae* and *proteus*, *Corynebacterium mallei*, *diphtheriae* and *necrophorum*, *Mycobacterium tuberculosis*, *Actinomyces hominis* and *bovis*, and with Crenothrix.

(4) Part of the gonidia of probably all species of bacteria, except those of the trichobacteria, are small enough to pass bacteria filter. They have been found to play an important rôle as filterable vira, "infective granules," or as so-called chlamydozoa, in diseases like trachoma, blenorrhoea non gonorrhoica, meningitis, scarlatina, lyssa, and various spirochaetoses. Multiplication as such seems to be the rule with the filterable gonidia, but under certain conditions, especially in the animal, reproduction of normal vegetative cells has been observed. The plasma in dead or dying cells of plants and animals generally offers the best opportunity for such an upgrowth; and the assumed transformation of cell granules into bacteria, which has been repeatedly proclaimed by adherents to the theory of heterogenesis, becomes easily explainable, as soon as the omnipresence and the peculiar behavior of the bacterial gonidia is taken into account.

(5) Those reproductive organs of the bacteria which have been called (pro tempore) regenerative bodies are produced either by the vegetative cell or by the symplasm. They are either globular, oval, pear-, or kidney-shaped, or more or less irregular, rod-shaped, and branched.

When developed by the vegetative cell, they may be found in a lateral or in a terminal position. The round regenerative bodies are able to multiply as such by fission and by budding, while the irregular forms either break up into round forms or reenter the symplastic stage. Pure growth of round regenerative bodies has been observed with *Streptoc. lanceolatus*, *Bact. pestis*, *septicaemiae*, *coli*, *cyanogenes* and *fluorescens*, *Bac. anthracis*, *Azotobacter* and *Amylobacter*, *Corynebact. mallei* and *diphtheriae*, *Mycobact. leprae* and *tuberculosis*. The uniform appearance of these bodies may sometimes cause difficulties in the diagnosis, especially in the case of diphtheria. Possibly several species of cocci will have to be reclassified as regenerative bodies of other species. This is very probable in regard to Nitrosococcus. Upgrowth of normal cells from the regenerative bodies is easily to be observed. It has been recorded with *Bact. pestis*, *coli*, *typhi*, *dysenteriae*, *radicicola*, *fluorescens*, and *cyanogenes*, *Bac. anthracis* and *Azotobacter*, *Vibrio cholerae* and other vibrios, *Spirillum rubrum*, various spirochaets, *Corynebact. mallei* and *diphtheriae*, *Mycobact. leprae* and *tuberculosis*. 1 to 4 sprouts may be produced by one regenerative body. While still connected with the parent cell the round regenerative bodies may be mistaken for products of plasmoptysis, and after being liberated for contaminating cocci, whereas the rod-like regenerative bodies of the micrococci may be confounded with bacilli or actinomycetes and the irregular regenerative bodies discarded as "involution forms." Instead of multiplying as such or germinating to new vegetative cells, the regenerative bodies occasionally develop to gonidangia or produce new vegetative cells by multiple fission. They are easily stainable, sometimes motile, and usually fairly resistant. The irregularities often observed in heating experiments with nonspore-forming bacteria are undoubtedly often due to the presence of regenerative bodies. Slow drying, a comparatively high concentration in the salt content of the substrates, and low temperatures have been repeatedly found to be favorable for developing a good growth of regenerative bodies.

(6) In some cases the round lateral or terminal regenerative bodies become unstainable and assume the character of so-called exospores, which take an intermediate position between the round regenerative bodies and the endospores. Their resistance is generally not higher than that of the former and distinctly lower than that of the latter. They have been observed with various vibrios and spirilla, as well as with the organisms of diphtheria, leprosy, and tuberculosis. In addition, however, they have been seen in a few cases with *Bact. pneumoniae*, *coli*, *typhi*, *acidi lactici*, *cyanogenes*, *Zopfii*, *fluorescens*, etc., and positive results secured in changing spore-free lactobacilli into spore-forming rods of the Mesentericus group and in reestablishing spore formation in asporogenous strains of butyric acid bacilli, make it very probable that bacteria producing such exospores represent, in fact, connecting links between nonspore-forming and spore-forming bacilli, and that their appearance in the cultures indicates the time when it becomes possible to induce a strain to develop its ability of endospore formation.

(7) Endospores can be produced besides by the vegetative cells, by regenerative bodies, as well as by gonidangia. The latter may contain two or more rudimentary endospores; and the formation of normal gonidangia is especially frequent in asporogenous strains of otherwise spore-forming bacilli. The polar endospores of *Bac. tetani*, *putrificus*, and of related species, are closely related to the terminal exospores. The same conditions which stimulate the development of the regenerative bodies are also favorable to endospore formation, which, however, usually takes place at a later time than the first-named process. If the endospore formation is suspended, the strains concerned become either similar to the regularly nonspore-forming bacteria, or to the Mycobacteria and Actinomycetes, which in their turn occasionally produce rudimentary endospores in their club-shaped gonidangia.

(8) Arthrospores are the result of a segmentation of the vegetative cells and of the transformation of these "joints" into fairly resistant bodies of globular shape. They are easily stainable and withstand drying better than heating. They are most frequent with Mycobacteria and Actinomycetes, certain Spirochaets and members of the Proteus group. Every arthrospore may produce 1 to 4 sprouts.

(9) Vegetative cells of bacteria sometimes transform themselves in their entirety into reproductive organs, called microcysts, by increasing their size, assuming a globular shape, and thickening their membrane. After a period of rest, they either resume directly their vegetative functions, or they germinate like spores, or they break up into 2, 3, or 4 segments which become vegetative cells. Sometimes they also transform themselves into gonidangia. Resistance and staining qualities are similar to those of the arthrospores, to which they are closely related. They have been found with micro- and streptococci, *Bact. proteus* and *aceti*, *Bac. anthracis*, *Azotobacter*, and other spore-forming bacilli, *Vibrio cholerae* and *proteus*, various Spirochaets and Mycobacteriaceae, and probably will be seen within all groups of bacteria, as soon as this point has received more attention.

III. FORMATION OF THE SYMPLASM AND THE REGENERATION OF CELLS.

1. GENERAL DISCUSSION.

Our observations relating to that part of the life cycles of the bacteria which we proposed to call the symplastic stage have been summarized in our first preliminary paper (*Löhnis* and *Smith,* 1916 *a*, p. 700) as follows:

> All bacteria studied live alternately in an organized and in an amorphous stage. The latter has been called the "symplastic" stage, because at this time the living matter previously inclosed in the separate cells undergoes a thorough mixing either by a complete disintegration of cell wall, as well as cell content, or by a "melting together" of the content of many cells which leave their empty cell walls behind them. In the first case a readily stainable, in the latter case an unstainable, "symplasm" is produced.
>
> According to the different formation and quality of the symplasm the development of new individual cells from this stage follows various lines. In all cases at first "regenerative units" become visible. These increase in size, turning into "regenerative bodies" which later, either by germinating or by stretching, become cells of normal shape. In some cases the regenerative bodies also return temporarily into the symplastic stage.
>
> The life cycle of each species of bacteria studied is composed of several subcycles showing wide morphological and physiological differences. They are connected with each other by the symplastic stage. . . . The transformation of spore-free into spore-forming bacteria seems to be dependent on the conditions acting upon the symplasm and regenerative bodies.

We pointed out in addition (*Löhnis* and *Smith,* 1916 *b*) that the facts recorded would certainly not have appeared so new and extraordinary as they did, if it had not (as a result of the prevailing "simplicity" theory) become a general habit to discard indiscriminately all evidence offered by the bacteria in this direction as being "merely dirt," or "simply slime," or "only detritus" resulting from bacterial "autolysis."

Very few references could be given at that time. But, as it was the case in regard to the pleomorphism of the bacteria and their different types of reproductive organs, search of the literature has furnished additional proof in abundance. The discussion of these facts, as recorded in the literature, though entirely neglected by the bacteriological textbooks to-day, will show anew how thoroughly modern bacteriology must be revised, before it will rest again on the solid ground of actual facts observed, instead of clinging to a narrow dogmatism, as developed during the last decades.

What we propose to call "symplasm" has already received several names. *Pineau* (1845) spoke upon a "substance granuleuse," *Perty* (1852, p. 106) about an "in Schuppen angeordnete Punktsubstanz," which occasionally formed globular agglomerations. *F. Cohn* (1853) adopted the term "zoogloea." *Lankester* (1876) furnished an excellent contribution upon "macroplasts or reproductive disks." *Haberkorn* (1882) introduced the expression "Bacteriophytom." *Marpmann* (1884) called the process "Protoplasma-Bildung." *W. Winkler* (1899) and *Almquist* (1917) used the name "plasmodium," the first-named author also the new term "Bakterioblast." *Růžička* (1903) classed the "zoogloea" as a "syncytium," and *Maher* (1910–1913) called the symplasm of the tubercle bacilli their "matrix."

We would, of course, readily give preference to one of these older terms if it would be equally distinct or better than ours. But "substance granuleuse," "Punktsubtanz," "Protoplasma-Bildung," "syncytium" and "matrix" can hardly come under consideration. The term "zoogloea" is being used so generally for all slimy agglomerations of bacteria that it has lost its specific meaning. The expression "plasmodium" implies motility, which is noticeable only in some cases. The "macroplast or reproductive disk," as described by *Lankester,* on the other hand, refers to a special discoid type of symplasm, which is a rather rare occurrence. So only *Haberkorn's* "bacteriophytom" and *W. Winkler's* "bacterioblast" would remain for

eventual adoption. But the latter term is very liable to collide with *Perty's* "blastia" (i. e., gonidia), and the former expression has been never used as far as I know except in a short preliminary paper, and it is hardly to be disputed that the terms "symplasm" and "symplastic stage" are more descriptive and more convenient.

The use of these new terms seems to be preferable also because of their adaptability to analogous occurrences in the life of other organisms. Some facts will have to be recorded on the following pages which indicate that undoubtedly with many of the lower organisms, but probably with the higher organisms, too, the symplastic stage of life plays an important, though hitherto little known rôle. As far as microörganisms come into view the sentence "Omnis cellula e cellula" is undoubtedly only partially true. But also with the higher organisms it does not seem to be so generally applicable as is often assumed.

That bacteria live alternately in various cell forms and in the amorphous symplastic stage, and that this fact furnishes the explanation of bacterial pleomorphism, as well as the experimental basis upon which the life history of the bacteria can be studied much more thoroughly and successfully than has been possible thus far, these conclusions apparently have not been reached before by any other author, evidently because even those who paid attention to the symplastic stage have worked with only one or a few species and had no opportunity to compare and unite their results with those secured by others, because nobody has ever tried to collect these data. The following discussion of the discovery of the symplastic stage will show conclusively how well our new observations agree with those secured already by earlier authors mostly at a time when the eyes were not yet mistrained to see in the microscope only the "normal, typical, legitimate" forms, and to overlook persistently all that which does not fit the theory.

(a) THE DISCOVERY OF THE SYMPLASTIC STAGE.

In the "Histoire naturelle des zoophytes" of *Dujardin* (1841, p. 20) the following passage is of interest:

> Quand . . . un infusoire n'est plus dans des conditions favorables à son existence, il se décompose par diffluence, c'est-à-dire que la substance glutineuse dont il est formé s'écoule en globules hors de la masse, laquelle, si les mêmes circonstances continuent à agir, se décompose tout entière . . . mais si par une addition d'eau fraîche ou d'un liquide convenable on change ces circonstances funestes, la reste de l'animalcule reprenant sa vivacité primitive, recommence à vivre sous une forme plus ou moins modifiée.

The "Recherches sur le développement des animalcules infusoires et des moisissures" by *Pineau* (1845 *a*) were more specific and more comprehensive. As the beginning of microscopic life he always found on the surface of organic substances submerged in water "une substance granuleuse, qui précède toujours l'apparition des êtres organisés des infusions, tant animaux que végétaux." He observed continuously the transformation of this granular substance into first immotile, later motile, bacteria and protozoa, as well as into molds. That he accepted this transformation as heterogenesis was, of course, not correct, but in agreement with the consensus of opinion at that time. His drawings, reproduced as figure 78 on Plate Q (from original figs. 8–27 on Pl. 4 bis), are of great interest, as is the following description given in a "Supplément" (1845 *b*) to these "Recherches:"

> On remarquait, en premier lieu, de petits amas de granulations dont les contours commençaient par être diffus; peu à peu ces amas devenaient plus nettement circonscrits, et ils finissaient par acquérir l'aspect de véritables monades, d'abord immobiles, puis douées de mouvement.—Le phénomène primitif du développement des cellules et des infusoires consiste essentiellement en une agglomération de granules.

Though primarily relating to other microörganisms, these observations are equally correct with regard to the regeneration of bacterial cells from the symplasm, while it must be left to mycologists and protozoologists to decide how far these old findings will be supported by the results of modern investigations upon the life history of these other microörganisms.

Perty (1852), to whom we owe the earliest detailed information upon the different types of bacterial reproductive organs, has also furnished very clear descriptions of the part played by the symplastic stage in the life of protozoa, as well as of bacteria. His observations upon

the formation of Podophyra and Actinophrys cells were illustrated by the drawing reproduced as figure 79 on Plate Q (from original figs. 9 and 10 on Pl. VIII) and described as follows (p. 74):

Im Winter 1848 nahm ich zum ersten Male Podophyra libera wahr, und zwar 5 grössere Exemplare von etwa 1/50′′′ Durchmesser lagen an einer Masse aus feiner Punktsubstanz gebildet, in welcher bis zu 1/400′′′ herab kuglige Zusammenballungen von Molekülen lagen, von welchen die grösseren immer deutlicher die Beschaffenheit teils von Podophyra, teils von Actinophrys annahmen . . . In den kleinsten dieser Zusammenballungen waren erst nur wenige Moleküle unregelmässig und locker vereinigt, in den grösseren zahlreichere zu regelmässiger Kugelgestalt mit allmählich sichtbar werdenden Strahlen; von diesen grösseren zeigten ein paar zitternde, hin- und herrückende Bewegung.

In old infusions, filled with bacteria and protozoa, *Perty* saw the motile bacteria agglutinate and transform themselves into immotile, crumbly, granular clumps of various shape, which when transferred into fresh solutions gave new bacterial growth (l. c., p. 109, 110). Most characteristic and essentially very correct is the following passage (l. c., p. 113), although the heterogenetic standpoint, which *Perty* shared with his contemporaries, is clearly noticeable:

Die organisierten Körper scheinen sich bei der Fäulnis aufzulösen und in eine unaussprechlich feine Punktsubstanz umzuwandeln, welche nicht in dem lebenden Organismen vorgebildet, sondern schon eine neue Construction ist. Diese Punktsubstanz (welche manchmal Neigung zeigt, sich in kuglige Agglomerate zu ballen . . . , auch bisweilen zitternde Bewegung zeigt) ist aber nicht eine durchaus homogene, sondern innerlich schon wieder verschiedentlich determiniert, so dass aus ihr Wesen verschiedener Art, namentlich Vibrioniden und Monadinen entstehen können.

Evidently the same fact has been studied by *F. Cohn* (1853) when he described the "Gallertkugeln" present in old bacteria infusions as being "ganz verschieden von den oberflächlichen Bakterienhäuten." "Zoogloea termo" was defined as "massae mucosae globosae, uvaeformis," and that later the floating films of bacteria usually have been called zoogloea is obviously not in accordance with these original findings and statements.

When *Robin* (1853) described his *Leptothrix buccalis* he also mentioned that its long cells were "réunis généralement, par la base, à une gangue amorphe granuleuse," which he thought to be the detritus of food remnants in the mouth, which, however, as will be seen later, may have been just as well flakes of symplasm not yet transformed into new threads. Later (1871) in his "Traité du microscope" the French author wrote concerning the same subject (p. 927):

Les nombreux granules, très fins, de volume uniforme, que le microscope montre dans le mucus, à la surface des cellules épithéliales, linguales, intestinales, dans beaucoup de déjections intestinales, ont un aspect très characteristique; elles ont, d'un auteur à l'autre, reçu des noms très differents (zoogloea, couche muqueuse primordiale, pellicule proligère).

It is, of course, not to be denied that this, as well as the earlier quotations given above, may also relate in part or wholly to agglomerations of bacterial gonidia and perhaps of regenerative bodies. Instruments and methods available at that time did not allow a clear distinction; even to-day such a task is not always easy. But the data to be given on the following pages will show that it is at least very probable that the symplastic stage has been already discovered by these early authors.

In the same manner as the bacterial gonidia proved to be of great value in supporting (apparently) the old theory of heterogenesis, as was discussed on pages 148–150, so naturally the amorphous agglomerations of bacterial symplasm can be mistaken even more easily for any other kind of vegetal or animal "slime," which by its ability to produce bacteria may be readily accepted as decisive, though in fact deceiving, proof of bacterial heterogenesis. This is the obvious reason why this hypothesis could be adhered to until recently by various authors. Their observations were usually fairly correct; but the absence of adequate knowledge upon the symplastic stage of the lower organisms allowed them to indulge in lofty speculations and made it impossible, on the other hand, to explain the facts recorded in an intelligent manner.

It was pointed out before (*Löhnis* and *Smith* 1916 *a*, p. 699) that especially those much doubted and disputed findings recorded by *Bastian* (1872–1914) now are coming under entirely new aspects. Many of his pictures prove beyond doubt that he, indeed, observed very carefully the upgrowth of cells from the symplastic stage. Those reproduced as figures 205–208 on Plate XVI (from original figs. 11 B and C, 12, and 13 on Plates IV and V, 1905, and fig. 33 A on Pl. XI, 1907) are especially characteristic and worthy to be compared with *Perty's*

and *Pineau's* drawings, as well as with other photographs shown on the following plates. That *Bastian's* experiments were faulty in many respects needs not to be pointed out, as he declared himself (1905, p. 184):

I emphasize the fact that the researches which I am about to detail have no pretence to be conducted in ways that are proper and usual in the great bulk of bacteriological inquiries.

Sterilization was often incomplete, and what he observed may sometimes have been dead cells, occasionally also silica conglomerates, though undoubtedly not so generally as *Payne* (1916) and *Onslow* (1917) are inclined to assume, as *Bastian* himself (1907, pp. 247, 275) was fully aware of this possible source of error. He also reported (1872, Vol. II, p. 209) that he saw the bacteria disappear, dissolving themselves into "a whitish refractive and homogeneous protoplasm," and more recently he added other interesting details concerning the formation of the bacterial symplasm and the regeneration of cells from it, which will be considered later. In view of all this, it is certainly not easy to understand how he could continue to assert (1903), p. 3):

The lower forms of life, both animal and vegetal, are ever springing up anew . . . from matrices wholly unlike themselves.

That *Bastian* did not become aware of the fact that he merely was dealing with the two manifestations of bacterial life is especially surprising when one considers what a great number of publications has been issued soon after his first book came out, all discussing the ability of the bacteria to form these "matrices" and to spring forth from them. *Osler* and *Schäfer* wrote in 1873:

In vielen Krankheiten befindet sich in dem Blute eine kleinere oder grössere Anzahl farbloser, granulierter Massen, die Grösse der weissen Blutkörperchen oft um viele Male übersteigend, und unter starken Vergrösserungen aus kleinen, blassen Teilchen zusammengesetzt erscheinend.

They also observed under the microscope that these substances were able to produce threads and motile bacteria.

That the "*Microsporon septicum*," described by *Klebs* (1872), behaves in an analogous manner was noticed by this author (1873), when he studied its growth in gelatin kept in Geissler's chamber. Besides regular colonies made up of rods, homogeneous yellow agglomerations were seen, sometimes spherical, sometimes of irregular outline showing protrusions "similar to the pseudopodia of amoebae." These plasmatic masses were seen to produce new bacteria, and, on the other hand, bacteria were seen to fuse together into such homogeneous plasma. Diphtheria cultures were found (*Klebs*, 1875 *a*) to contain small rods and "dark brown masses," homogeneous in the center, finely granulated at the outside, which were seen to transform themselves gradually into small bacilli, first at the edge, later in the center, too. In cases of endocarditis the same author (*Klebs*, 1878) noticed that the hyalin substances present were formed by micrococci. Stained with hematoxylin small granules became visible at the outside, while the center proved to be homogeneous, composed of round and of irregular agglomerations. Figure 210 on Plate XVII is a reproduction of *Klebs's* drawing (original fig. 3 on Pl. II). The author concludes:

Es scheint . . . nicht bezweifelt werden zu können, dass jene oft erwähnte hyaline Masse zum Teil aus den umgewandelten Schistomyceten besteht.

Furthermore, in 1883 *Klebs* pointed out in regard to tuberculosis, that *Koch's* bacilli are only one phase in the development of the causative agent, which presents itself in young inoculations as finely granulated masses, which later give birth to the bacilli. The following statement (1883 *b*, p. 131) is of great interest:

An isolierten Tuberkeln, welche in lufthaltigen, mikroskopischen Kammern der direkten Beobachtung zugänglich gemacht werden, sieht man diese feinkörnigen Massen aus dem Gewebe selbst hervorwachsen. Dieser Umstand sowie ihr Auftreten in den Kulturen beweist, dass sie einen integrierenden Bestandteil des Tuberkelorganismus darstellen, und diese Auffassung wird noch dadurch bestätigt, dass wie schon von *Koch* zugegeben, seine Bacillen in offenbar frisch wuchernden Tuberkeln oftmals nur in überaus geringer Anzahl gefunden werden. Andrerseits zeigt ihr constantes Nebeneinandervorkommen auch in möglichst reinen Culturen (ich habe die Anwesenheit der körnigen Massen auch in einer von *Koch* selbst hergestellten Cultur nachweisen können), dass beide Bestandteile gemeinsam zu dem Wesen des Tuberkelorganismus gehören.

The large hyalin globules noticeable in cases of rhinoscleroma within and without the cells were declared to be (*Klebs*, 1887, p. 271) "wahrscheinlich Überreste abgestorbener Bacillenhaufen."

Another set of analogous observations has been furnished simultaneously by *Letzerich*. In cases of diphtheria he found (1873–1876) large spherical or pear-shaped plasmatic bodies, which apparently were formed by a melting together of the bacilli lying side by side in the membrane, and which produced in their turn small coccoid bodies, which later were set free by rupturing the membraneous outside of these cyst-like bodies. Blood cultures furnished in addition large irregular agglomerations, sometimes showing amoeboid movements, occasionally uniting with each other or dividing into several parts. They also transformed themselves into "cocci," first at the edge, later in the center. The drawings reproduced as figure 80 on Plate R (from original figs. 5–10 on Pl. XII, 1876) look very queer and suspicious at the first moment. But we will have to consider later so much additional evidence, proving beyond doubt that, indeed, genuine bacteria may behave sometimes very much like Myxobacteria and Myxomycetes, that these drawings may find a place here, despite the fact that the trustworthiness of *Letzerich's* findings is undoubtedly much impaired by the manner in which he supported the most extravagant hypotheses à la *Hallier*. The plasma spheres of diphtheria, for instance, are said to develop occasionally to fungus spores, and the diphtheria organism is declared to be a "Tilletia diphtheritica." Obviously under *Klebs's* influence, a somewhat more sober standpoint was later taken by *Letzerich* (1880), who now also studied under the microscope in Geissler's chamber the transformation of the spherical "wax-like" masses of the "plasma cells" into normal colonies of bacteria.

Billroth (1874) found amorphous agglomerations in broth, serum, and various infusions, which he thought to be perhaps "plasmodia" and, on account of their showing occasionally a development of coccoid bodies, to be possibly the cause of a "eigentümliche Coccosentstehung aus einem zu einer Platte verschmelzenden Plasma" (l. c., p. 10). On the other hand, he also observed that in old cultures of bacteria and algae a dissolution of the cells took place. But apparently he did not think of any connection existing between these two facts.

In cases of variola *Weigert* (1875) discovered in the blood, as well as in various organs of the body, peculiar, granular, spherical, or cylindrical "Bakterien-Schläuche," which were embedded in amorphous masses produced by the surrounding cells, and which later themselves disappeared completely, becoming entirely homogeneous, or transforming themselves into smallest granules.

Probably the most important among the early contributions to the knowledge of the symplastic stage of the bacteria has been made by *Lankester* (1876) in the course of his investigations upon the red sulphur bacteria (*Bact. rubescens*). He noticed that repeatedly, always when the food supply became low, "macroplasts" or "reproductive discs" were formed, which under high magnification (×1,100) presented themselves to be either "truly homogeneous" or having a "minutely punctuate structure," or being regular colonies of globular cells, surrounded by a membrane. Further studies showed that the minute granules "indicate so many new units or centers of organization," and it is stated (p. 36):

> Just as we find exceptional cases in animal and vegetable cells in which a mass of protoplasm gives rise simultaneously to numerous nuclei, each of which becomes surrounded by a segregated mass of protoplasm and produces a numerous cell progeny by multicentral segregation, so it appears that in the large discoid macroplasts of Bacterium rubescens a formation of innumerable new plastids occur—not by a progressive division into two, four, eight, etc.—but by a simultaneous multicentral segregation.

It is, indeed, highly surprising, how such an excellent description of this very interesting process, which was accompanied by so characteristic pictures as those reproduced as figure 209 on Plate XVI, could later be entirely forgotten, and despite the various studies made by *Winogradsky* and by *Molisch* with the same or similar organisms nothing more was learned about these macroplasts, which, it is true, have no place within the narrow limits of the rigid dogma of bacterial monomorphism and constancy, which both authors felt obliged to defend vigorously. And yet, in addition to all other evidence, it is only necessary to compare *Lankester's* picture with the photograph of a Nitrosomonas "zoogloea" made by *Winogradsky* (1892),

which is reproduced as figure 270 on Plate XXI, to show at once that despite their conspicuousness it must have been difficult to overlook these things persistently.

But it is not less surprising that *Robert Koch*, too, just as he first saw and photographed the gonidia and regenerative bodies of various bacteria and later forgot all about them (cf. pp. 92 and 94), gave a faithful picture of the partially homogeneous, partially granular agglomerations of the symplasm, found by him in spreading abscesses in rabbits, on Plate I of his "Untersuchungen über die Aetiologie der Wundkrankheiten" (1878), reproduced as figure 211 on Plate XVII (from original fig. 8), but afterwards never returned to this subject. And not only this; he did not even hesitate (1884 *a*, p. 54) to "explain" *Klebs'* (1883) observations concerning the formation of symplasm by the tubercle bacilli by simply asserting that the unstainable masses seen by this author had been "serum." A glance at the quotation printed above suffices to demonstrate the utter inadequacy of this "explanation." An equally superficial "explanation" was furnished by *Loeffler* (1884, p. 431) in regard to *Klebs'* and *Letzerich's* discoveries. Their homogeneous plasmatic agglomerations are simply declared to have been normal bacterial "colonies" in the gelatin used, despite the very distinct differentiation, made by *Klebs* (1873) as well as by *Letzerich* (1880), between colonies and plasmatic "wax-like" agglomerations. Moreover, neither *R. Koch's* nor *Loeffler's* assumption gives any explanation for those homogeneous or granulated masses found by *Klebs, Letzerich, Weigert, Osler* and *Schaefer*, as well as by *R. Koch* himself, to be present within the body.

Nevertheless, from now on the symplastic stage of the bacteria was excluded from the "legitimate" bacteriology of *R. Koch* and his followers, as was the case with pleomorphism, with the gonidia, and with the regenerative bodies of the bacteria. During the following decades, however, many confirmative results have been gathered by independent workers, which, taken together, leave no doubt that the omission from the bacteriological textbooks of all data pertaining to this subject is quite unwarranted.

In 1880 and 1882 *G. A. Hansen* wrote upon "brown elements" occuring in leprous tissue which are filled either with a finely granulated mass or with normal rods. His descriptions, as well as his drawings, resemble those of *Klebs* and of *Letzerich* very closely, and they found an early confirmation in *Babes'* leprosy studies (1883), wherein it was ascertained that the tissue often contains "une masse homogène et granulée" while practically no microbes are visible.

Albrecht (1881) noticed in the course of his investigations upon the development of *Spirochaeta Obermeieri* that besides motile granules (gonidia) and spirochaets also "unförmliche Haufen von dunklen Punkten" were present in the blood, which continually changed their form.

At the same time *Fokker* (1881) noticed that *Bac. anthracis* produced within the body a similar finely granular "detritus," and further investigations (1882) led to the result that in 300 inoculation tests on mice in no instance bacilli were found, three times coccoid bodies, and in all cases in blood and liver

eine bedeutende Menge grobkörniges Material, das sich gar nicht färben und weder durch Alkohol noch auch durch Erhitzen am Glase ankleben liess.

Twenty years later *Fokker* (1902, pp. 16–26) returned to this subject, reporting that he found the "dissociation" of the anthrax bacilli in water, serum, and in broth to be especially pronounced during the first hours after having made the transfers. Comparative plating on agar gave, for instance, the following number of colonies:

At the beginning	721	2,000
After 1–2 hours	0	8
3–4 hours	3	.....
1 day	10,300	780
2 days	......	3,500

Concerning the regeneration of the bacilli it is assumed

dass sich aus diesem gelösten Plasma Granula verdichten und aus diesen Granula wieder Bacillen hervorgehen, oder aber, dass nachdem sich ein osmotisches Gleichgewicht ausgebildet hat, das Plasma wieder von den Gerüsten aufgenommen wird.

The latter possibility is considered to be more probable. As will be seen later, in fact both modes of reconstruction may take place.

Owing to *Fokker's* adherence to the theory of heterogenesis, it was unavoidable that in the same manner, as he accepted the participation of the gonidia in the reproduction of the bacteria as full proof of the heterogenetic origin of these organisms (cf. p. 149), so also the symplastic stage had to serve as an important part of his "neue Bakterienlehre." The "milk granules" and the flakes of "casein," which gave him (1901) "new" bacteria, have been undoubtedly flakes of symplasm and regenerative bodies growing out of it, as was discussed in our first preliminary paper (1916 *a*, p. 692). The photograph of such a flake of symplasm, studded with the round regenerative bodies of *Streptoc. lactis*, taken from milk, has been reproduced as figure 214 on Plate XVIII (from original fig. 33, *Löhnis* and *Smith*, 1916 *a*).

In his studies upon the "microzymas" *Béchamp* (1883) naturally also encountered the symplasm and saw it taking part in the reconstruction of cells. A characteristic drawing of his (original fig. 5, Pl. I) showing the regeneration of yeast cells from the agglomerations of "microzymas" in vinegar has been reproduced as figure 81 on Plate R. It should be compared with the analogous pictures made by *Pineau*, *Perty* and *Bastian* (reproduced as figs. 78 and 79 on Plate Q, and fig. 206 on Pl. XVI). The description given by *Béchamp* (l. c., p. 472) is worth quoting:

La mère de vinaigre est membraneuse et les microzymas y sont réunis par une matière unissante, hyaline. À mesure que les cellules apparaissent, les choses se passent comme si les microzymas consommaient en même temps et les aliments qui leur sont fournis par le bouillon sucré et la matière hyaline qui les unit, et s'agglomérant, sécrétaient la matière qui forme l'enveloppe, les parois de la cellule.

Very similar observations have been recorded by *Cocardas* (1884); and his drawings are much alike to those of the earlier authors. But the abstruse "nouvelles idées" presented in his paper make it, indeed, quite conceivable why the French "Société de Botanique" did not accept his contribution for publication.

That the "Bacteriophytom" of *Haberkorn* (1882) is identical with what we call symplasm has been mentioned above. It was always found in old cultures as large, compact, oval, or globular bodies with granular surface of different refraction, producing either "Körnerhaufen" (i. e. agglomerations of round regenerative bodies) which later grew up to rods, or directly regenerating numerous young bacilli which made the "Mutterboden" look "wie gestrichelt." Two of our photographs, reproduced as figures 256 and 257 on Plate XX (from *Löhnis* and *Smith*, 1916 *a*, original fig. 15, and 1916 *b*, original fig. 48), may demonstrate the correctness of these early observations.

Marpmann (1884, p. 44) was equally right when he wrote:

Unter Umständen löst sich eine ganze Familie oder ein Enzelwesen ganz in Schleim, Protoplasma auf. . . . Dieses Protoplasma kann wahrscheinlich unter günstigen Umständen wieder die ursprüngliche Spaltpilzform hervorbringen. Man findet solche Schleimmassen in allen älteren Kulturen, daher ist es wahrscheinlich, dass der Lebensprozess der Spaltpilze mit der Protoplasma-Bildung abschliesst. . . . Ob diese Schleimbildung stattfindet, wenn Spaltpilze in den gesunden tierischen Körper gelangen und sich nicht normal entwickeln können, ist nicht bewiesen, dagegen sehr wahrscheinlich.

"Les amas enkystés de bacilles" which according to *Babes* (1883) occur in "les tissus scléreux de tuberculose," and which were often found not to contain any rods, but instead of these "grains bien colorés, ronds ou cubiques, se rapprochant de l'apparence des sarcines," may well have been in part or wholly agglomerations of symplasm transforming itself into regenerative bodies. "La tuberculose zoogléique" of *Malassez* and *Vignal* (1883–1884) with its characteristic "masses zoogléiques de microcoques," which in old lesions reproduce the typical bacilli of *R. Koch*, eliminates all doubt, if there still should be any, that *Klebs'*, not *Koch's*, findings were the more correct and more complete ones. In their first paper the French authors state explicitly:

Il existe une parenté entre nos zooglées et les bacilles de Koch.

But in the second one they are again somewhat doubtful in regard to this point, and this probably was the cause why later authors sometimes declared this type of tuberculosis to have been pseudo-tuberculosis. The staining reaction of the "zoogloea" was found by *Malassez*

and *Vignal* (1884) to be variable, and it is pointed out specifically that such clumps may have often been mistaken for giant or mast-cells. *Amrusch's* (1886) observations "Über eine Zoogloea-Form der Tuberkel-Organismen" confirm fully the earlier discoveries. It is true that the German author was very anxious to point out that his findings had nothing whatever to do with those of the Frenchmen, because "his" zoogloea took the stain (weakly), while that of *Malassez* and *Vignal* is declared by him, quite contrary to their own statements, to have been unstainable. A study of his paper, however, reveals clearly, that he once more saw the melting together of rods to slimy, granular agglomerations, from which later new bacilli grew out; in addition to this he noticed, when studying the living material, that within these clumps continuous movements took place and the outlines changed frequently, exactly in the same manner as had been observed before by *Stricker*, whose results obtained with putrefying bacteria are reported in this paper.

In cases of "pseudo-tuberculosis" of guinea pigs *Eberth* (1885) found that instead of rods "micrococci" were present, especially in the liver, occurring in large clumps, stainable at the edges, unstainable in the center, just like *R. Koch's* septicaemia "micrococci." *Nocard* (1889) recorded similar facts, and *Zagari* (1890) thought himself to be justified, because he, like *Eberth*, *Pfeiffer*, and others, obtained slimy agglomerations of short rods (0.4×0.8–1.0μ), which he incorrectly calls micrococci, in cases of pseudo-tuberculosis of rodents, to "explain" the "tuberculose zoogléique," found by *Malassez* and *Vignal* in man, as having been "merely pseudo-tuberculosis," though he, of course, never saw the Koch bacillus develop from the zoogloea, as these authors had seen.

That spirilla may also enter the symplastic stage has first been recorded by *Finkler* and *Prior* (1884–1885). Old cultures of their vibrio furnished "körnige Massen, die man als Detritus bezeichnen könnte," which, however, transferred into new substrates (broth or gelatine) after 12–24 hours produced "ausserordentlich kleine Kommabacillen," slowly growing up to their normal size. Soon afterwards *Weibel* (1887) added to his description of a "Vibrio aus Nasenschleim" the following footnote (p. 469):

> Eine eigentümliche Beobachtung habe ich noch nachträglich gemacht. Präparate von einer 4 Wochen alten Agar-Cultur zeigen nirgends mehr intacte Stäbchen oder Fäden, sondern nur einen kleinkörnigen Detritus, der die Farbe schlecht annimmt—also das Bild abgestorbener und zerfallener Bakterien. . . . Wohl characterisierte Sporen findet man auch nicht. Und doch, wenn man aus diesser Masse in gewöhnlicher Weise auf neuen Agar überträgt, so wächst in 1–2 Tagen die üppigste Cultur. Nähere Untersuchungen hierüber werde ich nicht versäumen.

But in his later publication he did not touch this point again. Maybe he did not like to be attacked by *R. Koch* and his pupils in the manner as was done to *Finkler* and *Prior.*

Dowdeswell (1889–1890) found in his cholera cultures small masses of minute granules and sometimes of fine short filaments. Some of these masses were seen slowly moving around in an amoeboid or gyrating manner. The small granules contained therein reproduced vibrios and filaments by uniting and filling the cells, and it is also reported that—

> the cells of the filaments, in masses large or small, are seen to actually coalesce or be fused together, as if they were evolved out of a mass of primitive plasma.

Curiously enough, also this British author evidently was unacquainted with the analogous discoveries made by *Lankester* and the other early authors, who all had observed the same occurrence and had described it with practically the same words.

P. Ernst (1888) reported that he got prompt development of *Bac. xerosis* from the small granules visible in a "krümligen, pulpösen Einbettungsmasse," which was the only thing present in 3-months-old cultures. Already some years earlier *Hauser* (1885) had seen that the rods and filaments of his Proteus transformed themselves often quickly (within 24 hours) into a finely granulated zoogloea, wherein only minutest globules remained visible, and that later new rods and threads "germinated out of the clumps of zoogloea."

In the course of his leprosy studies *Lutz* (1886, p. 81) made the interesting drawings reproduced as figure 82 on Plate R, of what he, like later *P. Ernst*, called "Einbettungsmasse," and of which he says:

> Diese Einbettungsmasse spielt bei der Formation der leprösen Neubildung eine wichtige Rolle, da sie den grösseren Teil der Stäbchencolonie bildet.

Sometimes these slimy agglomerations looked to him like—

aufgelöste Nebelflecke in Gestalt durchsichtiger Wolken, die aus lauter Pünktchen und Tüpfchen bestehen.

In cases of rhinoscleroma *Cornil* and *Alvarez* (1885) found not infrequently within the giant cells, replacing the bacilli smaller or larger hyalin masses, which were stained more easily than the encapsulated bacilli. Good pictures of all intermediate stages are given in the paper, but the authors do not reach a definite conclusion, whether these masses were produced by the bacteria themselves or by the cells under the influence of the bacteria. That *Klebs* (1887) made analogous observations, has been mentioned before (p. 170), and in the textbook of *Cornil* and *Babes* (1890, Vol. II, p. 326) the question is taken up once more, but again no final answer is given, though the authors say (l. c., p. 327):

Existe-t-il une relation de cause à effet entre les microbes du rhinosclérome et les masses hyalines des grandes cellules? Cela nous paraît vraisemblable.

Billet (1890) made some interesting remarks upon the rôle played by the "état zoogléique" in the life history of *Cladothrix dichotoma* and of other bacteria, and stated (p. 215):

L'état zoogléique définitif . . . nous semble devoir constituer un caractère de premier ordre pour la différenciation des diverses espèces de Bactériacées.

Experiments with bacteria from the root nodules of leguminous plants furnished *Frank* (1890) sometimes peculiar colonies, formed by small motile "Schwärmer," which later developed to "Zoogloeahaufen," wherein the small bodies were visible "in kochender Wimmelbewegung." Figure 83 on Plate R illustrates these different types of growth (reproduced from original figs. 34 *a–c* on Pl. VIII).

Similar colonies were seen by *Prazmowski* (1890) in pure cultures of *B. radicicola*, as well as in the nodules themselves; they were surrounded, however, by a comparatively solid membrance, which was left behind, when the bacteria were liberated. The drawings made by *Morck* (1891), reproduced as figure 84 on Plate S (from original figs. 3 and 12 *e* and *f*), showing the clumps of plasma, which he saw to be formed by a melting together of the "bacteroids" in the root nodules of various legumes, make an interesting counterpart to *Lutz's* leprosy pictures, reproduced as figure 82. These clumps were found to be able to reproduce small rods, and on the other hand "granulated protoplasm" was seen to be present in the youngest part of the nodules, here forming small coccoid bodies, which later developed to normal bacilli.

If all the foregoing observations had elicited the interest, which they actually deserved, the important discoveries made by *Thaxter* (1892–1904) upon the Myxobacteriaceae undoubtedly also would have been valued by the bacteriologists in a more adequate manner, than it was generally their fate. Instead of being left aside as some curiosity, *Thaxter's* studies fully deserve to be kept in mind when planning thorough bacteriological investigations in the future. A short discussion of the relations existing between bacteria, myxobacteria and myxomycetes will be given at the end of this historical resumé.

In human, as well as in bovine, actinomyces "grains" *Crookshank* (1896) found the central portion "composed as a rule of a structureless core," but *Lachner-Sandoval* (1898), recording the same fact, pointed out that Gram staining makes small round Gram-positive bodies visible within the Gram-negative "detritus," which sometimes also may contain some pale shadows of former threads. Another observation, which the author was "unable to explain," because he, too, was not acquainted with the earlier findings concerning the upgrowth of new cells from such "granular detritus," i. e., from the symplasm, was very correctly described by him (l. c., p. 41) as follows:

Bei ganz jungen Individuen sieht man vielfach neben einem Faden oder auf dem Ende eines solchen . . . eine wolkenförmige Masse, die aus winzig kleinen, lichtbrechenden Körnchen besteht.

It will suffice to compare this description with one of our photographs, reproduced as figure 267 on Plate XXI (from *Löhnis* and *Smith*, 1916 *a*, original fig. 28) showing a young thread of our "yellow bacillus No. 41," developing from the symplastic stage, to understand at once the meaning of *Lachner's* "unexplainable" observation.

Some drawings made by *Niessen* (1898) of his diphtheroid "Syphilis-Bacillus," which were reproduced as figure 217 on Plate XVIII (from original fig. 13), should be compared with those of *Morck* and of *Lutz* given above. However, *Niessen's* contributions, as well as those made by *Münden*, are greatly impaired by the fact that the actual observations, discussed therein, are enshrouded by many fantastic ideas and unfounded hypotheses upon "cytoblast," "chthonoblast," the transformation of bacteria into crystals, etc., which have necessarily created a very suspicious attitude among the readers of these papers. But when we free the findings recorded therein, from these accessories, it becomes obvious that *Münden* has also seen the bacterial symplasm in its amoeboid and in its encysted forms, as well as the transformation of these hyalin masses into regenerative bodies of various shape, which ultimately reproduce the normal bacteria.

Very meritorious investigations upon the symplastic stage of bacterial life have been made by *W. Winkler* (1899); and it is hardly to be doubted that they would have attracted much more attention if they had not been discussed rather summarily in one short paper, to which merely drawings were added, which can not convey an adequate idea of what the author found and of what is really to be seen in such experiments. Some of them are reproduced as figure 212 on Plate XVII. In liquid as well as on solid substrates, in mixed and in pure cultures, *W. Winkler* always met with smaller and larger clumps of finely granulated or homogeneous plasma, sometimes inclosed within a solid membrane, in other cases naked and showing amoeboid movements like a plasmodium. Often these clumps assumed a "brain-like" structure, and a small central body ("Mittelpunktkörperchen") became visible within each lobe. One of our photographs, reproduced as figure 231 on Plate XVIII (from *Löhnis* and *Smith*, 1916 *a*, original fig. 12), may serve as an illustration. The transformation of these plasmatic masses into bacteria was directly observed under the microscope and (l. c., p. 576) described as follows:

Die dem Rande zunächst liegenden Granula ordneten sich in Reihen; die einzelnen Körner umgaben sich mit Plasma, rückten auseinander, schwollen an, streckten sich und wurden nach und nach zu Bakterien.

Two of our photographs, reproduced as figures 215 and 216 on Plate XVIII (from *Löhnis* and *Smith*, 1916 *a*, original fig. 32: *Streptoc. lactis*, and 1916 *b*, original fig. 56: *Microc. candicans*) may be compared in this respect.

Sometimes the first cells formed showed very irregular outlines; they were triangular, spindle-shaped, oval, cubic, or more or less irregularly curved. Already in 1880 *Neelsen* has pictured such an occurrence in the drawing reproduced as figure 85 on Plate S (from original fig. 10 on Pl. XI).

Clumps of symplasm of different size were frequently seen by *Winkler* in colonies, especially in those imbedded within the substrate, and here the symplasm was often inclined to send out thread-like protrusions, which the author called "filidia." These filidia may produce more or less normal bacteria, either by contraction or by segmentation, as shown in the right part of figure 212 on Plate XVII (reproduced from *W. Winkler's* original fig. 41), or by furnishing the material for their formation within the more or less solid membrane of the filidium, as illustrated by the two sketches in the upper center of figure 212 (reproduced from original figs. 34 and 35). Sometimes large round bodies, called "macrospores," were seen to grow in the symplasm, or within broad filidia, which acted as "sporangia"; the drawings in the lower left part and in the center of figure 212 (reproduced from original figs. 48 and 50) picture these two possibilities. It is beyond doubt that these "macrospores" of *W. Winkler* are identical with our large round regenerative bodies, whose frequent upgrowth from the symplasm will have to be discussed later.

As far as I know, only one author, *Růžička* (1903), has paid attention to and has continued *Winkler's* work. Unfortunately, he restricted his observations to the study of mixed infusions and buried his data in a paper "Ueber die biologische Bedeutung der färbbaren Körnchen des Bakterieninhaltes." He followed continuously the dissolution of the bacteria cells and their reconstruction from the plasmatic masses, which he calls "zoogloea," and concludes:

Es kann als gesichert gelten, dass die Zoogloea ein Syncytium darstellt, in welchem die beiden Komponenten, die geformten Elemente und das strukturlose Plasma die Fähigkeit besitzen, in einander überzugehen.

But there still remain some more recent observations, all made quite independently, which also represent important contributions to our subject.

When N. K. *Schultz* (1901 *a*) made her investigations upon the longevity of the gonidia of *B. pestis* and their participation in the life cycle of this organism, she noticed that in old cultures minute granules were present, imbedded in weakly staining flakes, which after being transferred to fresh substrates, first produced agglomerations of globular bodies, which soon after grew up to normal rods; but 14 days later the pale flakes with their minute granules appeared again and replaced the vegetative cells. The figs. 218–221, reproduced on Plate XVIII (from original figs. VII–IX and XII), illustrate these changes very clearly. However, the Russian bacteriologist was not aware that she was facing the symplastic stage of the plague bacillus. The flakes inclosing the granules were thought to be "le précipité floconneux du bouillon," and of course, especially in the several years old cultures, such an occurrence had been quite probable. But the very pronounced similarity between the old and the new flakes proves that this was not the case. The artist (*Ivanoff*), who made the pictures and merely copied what he saw, without being blinded by any prejudice, showed very clearly that the new flake (fig. 221) is formed by the residues of the agglutinated cells, which had become unstainable. Moreover, it will suffice to compare these pictures with others reproduced on our plates to feel convinced that also in this case it was the symplasm, not some dead precipitate, which made such luxuriant upgrowth possible.

The actinomyces-like buds which *Lignières* and *Spitz* (1902) found growing out of the hyalin homogeneous mass, which formed the grains in the pus of cases of actinobacillosis, are very similar to those of *Metchnikoff's Pasteuria ramosa*, as may be seen from the drawings of the first-named authors, reproduced as figure 213 on Plate XVII. It is true that *Metchnikoff* did not pay any special attention to the fact that the characteristic clubs of his Pasteuria were produced by flakes of hyaline symplasm, but a photograph made by *Roux*, which was added to *Metchnikoff's* (1888 *b*) drawings, and which is reproduced as figure 222 on Plate XVIII, proves this point.

A bacillus, evidently related to *B. pneumoniae*, if not identical with it, was studied by *Jehle* (1902) with the result that hardly any normal cells were seen in 5–8 days' old cultures, but numerous crumbly pale masses and flakes, which after being transferred to new substrates promptly reproduced polymorphous cells.

With regard to leprosy *Pernet* (1902) reached the conclusion that the "gloeal masses," which he, like G. A. *Hansen* (1880–1882), *Babes* (1883), and *Lutz* (1886), found within the tissue cells, are not products of degeneration, but "a phase in the parasite's life history, a resting stage, during which it prepares for further proliferation," and he pointed out that clinical observations are in good agreement with this view.

Fuhrmann's (1906–1908) results with *Pseudomonas cerevisiae* are very similar to those recorded by *Schultz* with *B. pestis*. Here again the "detritus" containing minute granules, showed itself to be able to reproduce new vegetative cells after long periods of rest. A good photograph, published in the second paper (1908, original fig. 5 on Pl. I) and reproduced as figure 238 on Plate XIX, exhibits the typical appearance of the symplasm with its regenerative units, regenerative bodies and new rods.

Some very important contributions to our subject have been made by *Rosenbach* (1909), when he studied his polymorphous Erysipelothrix (*Bac. erysipeloides*). The four photographs reproduced as figures 239–242 on Plate XIX (from original figs. XIV, 6; XII, 2; XIII, 2 and XII, 1) are of special interest. The rods, whose normal appearance was shown in figures 26 and 27 on Plate III, agglomerate and enter into granular dissolution (fig. 239); the end products are visible in figure 240. Occasionally these granular clumps may reproduce fine threads, as shown in figure 241, or even a distinctly mycelial growth may spring forth from them, like that in Figure 29 on Plate III. Sometimes, however, the dissolution of the rods ends with the formation of completely homogeneous masses, which may surround themselves with rather solid membranes, thus forming large globules, as shown in 270-fold magnification in figure 242. This encystment of the symplasm is of great interest when compared with those old reports,

made by *Letzerich* and other early bacteriologists upon the production of large cysts by typical bacteria closely resembling the cysts of certain Myxobacteriaceae.

The symplastic stage of the tubercle bacillus, so well studied by *Klebs* (1883) and by *Malassez* and *Vignal* (1883–84), but so flatly rejected by R. *Koch* (1884), was once more discovered and fairly thoroughly investigated by *Maher* (1910–1913). He became aware that it is especially due to the ability of this nonacid-fast "matrix" to reproduce many different forms of various staining reactions why old cultures of tubercle bacilli are so much inclined to furnish cells of very variable size, shape, and pigmentation. According to our own experience the following statement, made in *Maher's* second paper, allows a wide generalization:

From this matrix it is possible to grow coccal and bacillary forms that vary in morphology, in acid resistance, and in chromogenic power, according to the variance in the age and vegetative energy of the tubercle bacilli that composed the matrix, and according to the variance in the technique to which the matrix is subjected.

At least partially correct were also the findings of *Herzog* (1913) concerning the slimy dissolution of gonococci, or of whole colonies of these organisms, into a yellowish, transparent mass, which at first still contained some minute globular bodies, later, however, became either entirely homogeneous—in this case its was declared to be dead—or transformed itself into oval or globular "giant forms."

That *Meirowsky* (1914 *b*) in his investigations upon the development of the bacteria frequently met with the symplastic stage of various bacilli, spirilla, and spirochaets is clearly demonstrated by a number of the pictures accompanying his paper. For instance, the sketches of *Spirillum rubrum*, reproduced as figure 86 on Plate S (from figs. 4 and 5 on Pl. V *b*), and some of the illustrations of "Doldenbildung," shown on Plate XIV, leave no doubt upon this fact. But *Meirowsky* himself thought these "umbels" were closely connected with the "bud formation," caused by the gonidia leaving the cells, and he stated at first (p. 9) explicitly:

Die Dolden sitzen stets am Ende des Bazillus und stellen eine feine wolkige Masse dar, die aus zahlreichen sehr kleinen, stark lichtbrechenden Körperchen besteht.

Later (p. 16), however, he admitted that the "umbels," made up of small granules embedded in a zoogloea-like matrix, were often found without being attached to a rod, and that he also saw all intermediate stages between these masses and new vegetative cells. The size of such agglomerations exceeds that of a bacillus or of a spirillum frequently so manifold, that it would be quite inconceivable how they might develop from one single cell; the opposite process is, no doubt, much more probable.

Some very characteristic photographs, published by *Almquist* (1916–1917), demonstrating the development of new cells from what he calls bacterial "plasmodia," have been reproduced as figures 243–247 on Plate XIX (from original figs. 12 and 22, 1916, and Nos. 5, 6, and 12, 1917). Figure 243 presents the upgrowth of *B. typhi;* besides fairly normal rods, large yeast-like forms and peculiarly slimy threads are visible, "in statu nascendi." Figure 244 shows the round regenerative bodies of *V. cholerae* being formed within a flake of symplasm. This picture should be compared with figure 238 (symplasm of *Pseudomonas cerevisiae Fuhrmann*). Figure 245 was made from a single cell culture of *B. diphtheriae;* together with figure 246, *B. acidi propionici c*, it exemplifies the possibility of very irregular forms consolidating themselves out of large and small flakes of symplasm. Figure 247 pictures the symplasm of *Almquist's Bact. antityphosum* (cf. p. 147); it may be compared with figure 216 on Plate XVIII, presenting *Micr. candicans* in the same phase of its life cycle, and also with figure 223 on the same plate, which is a reproduction of a picture made by *Kellerman* and *Scales* (1916) of the first beginning of new growth of *B. coli* from the symplasm. Another photograph of the same authors, reproduced as figure 224 on Plate XVIII, illustrates once more the concentration of the pale granular mass first into an unsharp slimy thread, like those photographed by *Almquist* of *B. typhi* (fig. 243), and the progressive consolidation of parts of this thread into normal, deeply staining rods. Two other coli pictures, made by *Kellerman* and *Scales* (1916) and reproduced as figures 44 and 45 on Plate IV as an illustration of the pleomorphism of this

species, will now also be better understood as to their true meaning. They show clumps of the large yeast-like cells, so frequently originating in and from the symplasm, and another example of such broad threads, to be compared with *W. Winkler's* "filidia."

The summary of the results of our own preliminary studies upon the symplastic stage of representatives of various groups of bacteria has been given on page 166. It may be added here that by some special experiments (*Löhnis* and *Smith*, 1916, *a*, p. 679) the fact has been definitely established that not only in old, but also in very young, cultures the formation of symplasm may take place in accordance with the tendency of the bacteria to live alternately in an organized and in an amorphous stage. Some of our photographs, illustrating the various steps leading from cells to symplasm and back to cells of the same or of a different type, have been reproduced as figures 225–233 on Plate XVIII, figures 250–261 on Plate XX and figures 262–267 on Plate XXI. As a detailed discussion of these pictures will better find its place on the following pages, it may suffice to mention here that figures 225-231 on Plate XVIII and figures 250-258 on Plate XX were all made from Azotobacter. Figure 232 (Pl. XVIII) and figures 259–263 (Pls. XX–XXI) illustrate different phases in the life cycle of *B. fluorescens*. A flake of symplasm of *B. subtilis* is shown in figure 233 (Pl. XVIII) for comparison with figure 230. The upgrowth of *Sarcina flava* is demonstrated by figure 264 (Pl. XXI). Figure 266 shows peculiarly pointed cells of *B. malabarensis*, whose large gonidia break out before melting together to the symplasm. A thread of the "yellow bacillus No. 41" growing up from the symplasm is visible in figure 267.

It needs hardly to be emphasized that these photographs furnish fairly accurate illustrations to several of the early descriptions, mentioned above, or somewhat superior counterparts to the rather primitive drawings, made by the earlier authors. It should be pointed out, however, especially for those readers who have not yet seen such preparates under the microscope, that even the best photographs can only convey a very incomplete impression of the actual appearance of this type of growth. Large flakes or clumps of symplasm, which make the most interesting object under the microscope, can not be photographed at all. And even so many parts of the smaller agglomerations are necessarily out of focus, that the flat photographic picture is always very inferior to the bright and plastic appearance of the symplasm under the microscope.

But in one direction these photographs will hardly leave any doubt, viz., that a thorough study of this particular phase of the life cycles of the bacteria will supply us with very valuable and much needed information upon the occurrence of different cell forms, the real significance of so-called involution forms, the appearance and disappearance of variations and mutations, and many other data, which could not be obtained with the customary methods of investigation.

Cultures showing "autolysis" or "granular decomposition" of their cells are usually discarded as speedily as, or even more lightly than those producing "involution forms," much to the disadvantage of bacteriological science. From the descriptions furnished by authors like *Ermengem* (1885, p. 20), *E. Klein* (1885, p. 111), *Gamaleia* (1900 pp. 27, 154), *Kruse* (1910, p. 20), *Rettger*, *Berman* and *Sturges* (1916), and many others, it may be safely concluded that more thorough tests would have demonstrated, that also in these cases "degeneration" would have been supplanted by "regeneration," as soon as suitable conditions for the revival of cell life had been established. It is, of course, self evident that permanently adverse conditions must end all life, but "autolysis" of the bacteria is by no means equivalent to death; in fact, it enables the living matter to readjust itself and to reenter cell life in a better adapted modification. Every experienced bacteriologist knows that careful testing will bring many cultures back to good growth, which on superficial examination would be declared dead. That "autolysis" may be followed by renewed development has been observed, e. g., very clearly by *Malfitano* (1900) in his experiments upon "La bacteriolyse de la bactéridie charbonneuse" in full agreement with those made by *Fokker*, which were discussed on p. 171. A few hours after the bacilli had been transferred into distilled water only an "amas de débris informes" remained, but the author adds:

Le phénomène est très net, bien que, dans ces conditions de nouvelles bactéridies puissent se former.

Kruse (1910 p. 21) also says:

Unter Umständen tritt in denselben Mitteln (i. e. in old cultures, serum, etc.) Bakteriolyse und Wachstum neben oder nacheinander auf, indem nämlich die durch Selbstverdauung schon zugrunde gegangenen Bakterien den übrig gebliebenen den Nährboden . . . verbessern . . . oder . . . im Serum die Alexine neutralisieren.

A more complete knowledge of the facts recorded by the earlier authors would probably have replaced the hypothesis in the last part of this statement by a more correct reference to the bacterial symplasm.

That the bacteria are to be frequently found in their amorphous stage in vivo as in vitro has been indicated by the quotations taken from the publications of *Osler* and *Schäfer* (1873), *Letzerich* (1873–1876), *Weigert* (1875), *Klebs* (1878–1887), *R. Koch* (1878), *G. A. Hansen* (1880–1882), *Albrecht* (1881), *Fokker* (1881–1882), *Babes* (1883), *Malassez* and *Vignal* (1883–1884), *Cornil* and *Alvarez* (1885), *Eberth* (1885), *Amrusch* (1886), *Lutz* (1886), *Nocard* (1889), *Crookshank* (1896), *Lachner-Sandoval* (1898), *Lignières* and *Spitz* (1902), and *Pernet* (1902). More recently renewed attention was given to this point. A photograph made by *E. de Negri* (1916) of the amorphous masses found in granulom tissue, caused by a Corynebacterium, has been reproduced as figure 237 on Plate XVIII. What *Mallory* and *Medlar* (1916) described and pictured as "clumps of bacilli," taken from the tonsils in cases of scarlet fever, show very clearly their symplastic status, when we compare the photograph reproduced as figure 248 on Plate XIX (from original fig. 23 on Pl. XX), for instance, with figures 216, 246, 247 and 254 on Plates XVIII–XX. The same holds true in regard to a photograph made by *Mellon* (1917, original fig 5, Pl. 2) of "a colony of diphtheroid bacilli lying in the interstitial tissue of the lung," which was reproduced as figure 249 on Plate XIX. In cases of poliomyelitis, *Rosenow, Towne* and *Wheeler* (1916) found often in tonsillar abscesses "a peculiar gelatinous opalescent material from which the peculiar Streptococcus was isolated in large numbers." And when *Wade* (1918) studied an unclassified chronic Philippine ulcer, he obtained results which are in complete agreement with the numerous findings mentioned above, although according to the author's own judgment his "hypothesis departs radically from orthodox views." He says:

"Essentially it appears as if the differentiated demonstrable parasitic element in a mycotic lesion may give rise to a derivative substance, morphologically not differentiated and perhaps even quite amorphous, that, unlike the known toxins, soluble or insoluble, is by itself more or less viable and may be capable, to a certain extent at least and under certain conditions, of persisting as such and even of increasing or growing."

This "substance or body" was named by *Wade* "cryptoplasm," while for the large round bodies, which were again seen to develop from it, the term "cryptococcus" was introduced.

It is to be expected with certainty that more confirmative results will be secured as soon as the hyalin and amyloid substances of the body will be made the object of new studies along these lines. Descriptions published by *Lubarsch* (1903) leave no doubt that appearance and staining reactions are very much alike in both cases, and though he does not refer to a participation of microorganisms in the formation of these substances, this has been done already in 1878 by *Klebs* and in 1885 by *Ziegler*, who pointed out (1885, p. 285) that epithelial cells, when attacked by bacteria, swell up and liquefy or degenerate into homogeneous lumps or granular detritus. To what degree the cells of the host on the one side, and those of the parasite on the other, are to be made responsible for the outcome apparently nobody has ever tried to decide. But that the living plasmatic substances of the higher organisms, especially those building up the animal tissue, are equally able to enter and to pass through such a "symplastic" stage as the bacteria do, has been pointed out by *Robin* about half a century ago, according to *Béchamp* (1883, p. 543), in the following statements:

En anatomie génerale on appelle blastème ou cytoblastème des espèces de substances amorphes liquides ou demiliquides, soit épanchées entre les éléments anatomiques préexistantes dans un tissu ou à sa surface, soit interposées entre des éléments qui naissent à leur dépens au fur et à mesure de leur production au sein ou à la surface d'un tissu.

Dans le blastème prennent ou peuvent prendre naissance des éléments anatomiques, normaux ou morbides (granulations moléculaires, fibres, tubes, cellules, etc.).

Le blastème est une matière complètement homogène, amorphe, sans structure.

And quite recently *Burrows* and *Neymann* (1917) reported upon their "Studies on the Metabolism of Cells in vitro" as follows:

Growth associated with mitotic cell division is seen only in (tissue) cells which have become passively placed at the interspace between certain insoluble substances and the medium. These substances are liberated from the cells when they are removed from their normal habitat to an oxygen containing plasma or salt solution. The substances are almost transparent, their refraction is not very different from that of the original medium and they accumulate at the surface of the medium to form a membrane. They are liberated in large amounts from a tissue fragment rich in cells.

A cell brought in contact with the surface of this transparent substance adheres to it and flattens over its surface. Such a cell grows and divides by mitosis when oxygen is present and the waste products remain below a certain concentration.

A single isolated cell when placed in a drop of fresh plasma does not grow and divide.

It is hardly to be doubted that a close study of the symplastic stage of bacterial life will yield information of considerable value for general biology. The formation of new cells directly out of the amorphous plasma can perhaps in no case be better observed than with the bacteria, although lower fungi, as well as protozoa, may also furnish excellent objects for such investigations, as had been noticed by *Pineau* and *Perty* a long time ago, according to their studies discussed on pages 167–168.

When referring to *Thaxter's* Myxobacteriaceae (on p. 174) it has been pointed out that the more complete knowledge of the life cycles of the bacteria undoubtedly establishes much closer connections between these two groups of organisms, as well as with the Myxomycetes. *W. Winkler* (1889) concluded from his observations that the bacteria are related to Myxomycetes as well as to Amoebae and that the Myxobacteria are true bacteria. In 1866, *Woronin* placed the root-nodule organism (*B. radicicola*) in the neighborhood of Plasmodiophora, as did later *Kny* (1879) and *Prillieux* (1879). *Schroeter* (1886, p. 134) and *Atkinson* (1893) class it among the Myxomycetes; *Zukal* (1897), *Stefan* (1906), *Jörgensen* (1911), and *Pinoy* (1913) emphasized its relationship to the Myxobacteriaceae. It is not to be disputed that the formation of spores and cysts by the Myxobacteria, as it has been described in the publications of *Thaxter* (1892–1904), *Zukal* (1897), *Baur* (1905), *Quehl* (1906), *Kruyff* (1908), *Vahle* (1909), *Jahn* (1909–1911), and *A. L. Smith* (1913), at the first moment seems to have very little in common with the general behavior of the bacteria. But it must never be overlooked that the experimental conditions under which the bacteria are nearly always kept and studied also do not allow the Myxobacteria to develop in their characteristic form, as has been shown, for instance, by *Quehl* and *Vahle*. The small *Bac. helixoides* (0.6×2–4μ,) isolated by *Muto* (1904) from saliva, which grew on the plate in colonies made up of rods at the edge and oval forms in the center and sent out slimy protrusions creeping forward like snails, undoubtedly has been a maltreated Myxobacterium. *Jahn* was certainly right when he wrote:

Die den Myxobakterien eigentümliche Form der Coloniebildung ist auch bei den Bakterien nicht so ungewöhnlich, und sie würde auch den Bakteriologen noch vertrauter sein, wenn sie mehr gewohnt wären, die Bakterien unter ihren natürlichen Lebensbedingungen zu beobachten.

A bacillus isolated by him showed in a nutrient solution a behavior very similar to that of Myxobacteria:

Verschlechtern sich die Existenzbedingungen, so vereinigen sich die Bacillen zu einem dichten Haufen und tanzen lebhaft wie ein Mückenschwarm durcheinander. Dann kommen sie allmählich zur Ruhe, sondern Schleim ab und bilden eine characteristische Colonie aus rundlichen, verkürzten Individuen.

When studying the "zoogloea" stage of the bacteria in 1877 *R. Koch* also reported (p. 415) to have seen the cells within the zoogloea agglomerate into groups of 10–12 individuals and to enter spore formation. *Zikes* (1916) observed on dry gelatin a growth of bacteria, as well as of yeasts, which was microscopically as well as macroscopically similar to that of certain myxobacteria.

That the spore formation of the Myxobacteriaceae is fundamentally identical with the production of arthrospores and microcysts of the bacteria has been discussed on page 123. The same holds true in regard to the agglomeration of the vegetative cells and their slime production preceding the encysted stage of the myxobacteria, and the symplastic stage of the bacteria. As figure 87 on Plate S a drawing made by *Baur* (1905) of *Myxococcus ruber* in

the beginning of fructification has been reproduced (from original fig. 3 on p. 113). It should be compared with one of *Rosenbach's* photographs, reproduced as figure 239 on Plate XIX, showing *B. erysipeloides* before entering the symplastic stage. The more or less complete dissolution of the vegetative, as well as of the reproductive, cells of the bacteria forming the symplasm obviously constitutes the most pronounced difference although perhaps a similar behavior may still be discovered among myxobacteria, as well.

The encystment of these agglomerations is also by no means absent among the bacteria. The cyst of Polyangium, drawn by *Zukal* (1897, original fig. 8) and reproduced as figure 88 on Plate S, makes a counterpart to some of the old sketches of bacteria found in cases of diphtheria by *Letzerich* (1876, reproduced as figs. 68 and 80 on Pls. P and R) and of a leprosy zoogloea, published by *G. A. Hansen* (1880, original fig. 10). The "macroplasts" of *Bact. rubescens*, studied by *Lankester* (1876) and reproduced as figure 209 on Plate XVI, the "zoogloea" form of Nitrosomonas, as photographed by *Winogradsky* (1892) and reproduced as figure 270 on Plate XXI, the Asococcus of *Billroth* (1874) and *F. Cohn* (1875), the Clathrocystis of *Cohn* (1875), the Ascobacteria of *Van Tieghem* (1880), the *Micrococcus botryogenus* of *Rabe* (1886), the Amoebobacter and Thiocystis of *Winogradsky* (1888, pp. 60–78), the Ascobacterium of *Babes* (1895), the Ascobacillus of *Moreno* (1901), as well as the "bacteriocysts" of *Müller-Thurgau* (1908), which are to be discussed on the following pages, indicate all very clearly that large encysted agglomerations of cells are not at all uncommon among the bacteria. Even the homogeneous symplasm may encapsulate itself, as was shown by *Rosenbach* (1909) in the photograph reproduced as figure 242 on Plate XIX. That it will mostly depend on the environmental conditions whether or not such macrocysts will be formed by the bacteria, may be safely assumed, though hardly any experimental results are available at present in this direction. *Pinoy* (1913) pointed out that symbiotic (or antagonistic?) effects may act as stimulants in this direction; and, indeed, we should never forget that our pure cultures on standardized media will often fail to exhibit the characters shown by the mixed microflora under natural conditions.

That the bacterial symplasm is able to reproduce either round regenerative bodies or directly vegetative cells is another parallelism to the behavior of the myxobacteria, which pass their resting stage either as spores or as vegetative cells. But with the bacteria both modes of regeneration occur apparently with every species, while in the latter case a more distinct differentiation has taken place.

The occurrence of bacterial plasmodia, showing amoeboid movements, indicates relations existing between bacteria and Myxomycetes, as was pointed out by *W. Winkler* (1899). *De Bary* (1884, p. 477) thought the Myxomycetes should be separated from the fungi and should be called, together with the Acrasiae, Mycetozoa. However, as *Henneberg* (1904) has demonstrated more recently, amoeboid stages may be also found with true fungi (yeasts); on the other hand, amoeboid movements of the bacterial symplasm do not seem to be a general character, and more thorough studies very probably will reveal many analoga to the bacterial symplastic stage among protozoa, as well as among fungi and algae. Therefore the relations existing between bacteria and protozoa should not be too much enhanced on account of this one point.

(b) FORMATION AND APPEARANCE OF THE SYMPLASM.

According to the observations made by *Lankester* (1876), *W. Winkler* (1899), *Rosenbach* (1909), and *Löhnis* and *Smith* (1916 *a* and *b*) the formation of the symplasm always takes place in two phases: First, the bacteria agglomerate to smaller or larger clumps; second, the cells dissolve more or less completely to a crumbly or slimy mass, assuming the shape of flakes, irregular clumps, or regular spheroid bodies, and being sometimes endowed with amoeboid motility.

Apparently all species of the bacteria and all kinds of vegetative cells, as well as of reproductive organs, are able to enter the symplastic stage. It occurs both in old and in young cultures, dependent on internal as well as on external conditions.

A so-called pseudo-agglutination has been frequently noticed in connection with agglutination tests; it has been discussed by *Savage* (1901), *Escherich* and *Pfaundler* (1903, p. 341), *Hiss* and *Zinsser* (1914, p. 231), and others. *Hewlett* (1902, p. 143) found that "agglutinins" were present in old broth cultures of typhoid bacilli; filtrates obtained therefrom powerfully agglutinated the bacilli in fresh broth cultures. *Nocht* and *Mayer* (1907, pp. 18, 33) report that spirochaets often agglomerate when kept for a longer time at low temperature or in serum, that the agglomerated cells occasionally fuse together in the center, and that sometimes "desagglomeration" was observed. That similar clumps of spirochaets may be also found in the tissue is indicated by a photograph made by *Flexner* (1907) of "colony-like" masses present in the skin of a macerated syphilitic foetus. *McFarland* (1916, p. 721) says referring to this picture: "The dense aggregation of organisms may indicate agglutination." There is no doubt, however, that the agglomeration preceding the formation of the symplasm is essentially different from the typical agglutination, though both processes present a very similar appearance. Agglutination is, according to the careful review published by *Köhler* (1902), prominently a physico-chemical reaction, whereas the active gathering of the cells, when entering the symplastic stage, makes it quite evident that in the first place a biological cause is active in this case, though external, physical as well as chemical, factors will naturally also exert their influences, hastening or retarding the agglomeration of the cells.

The dissolution of the united cells leaves either the empty cell walls as "shadows," but still clearly visible, in the field, or they, too, are disintegrated and participate in the formation of a more or less homogeneous symplasm, which often becomes entirely amorphous, hyalin, and highly refractive. Our photographs reproduced as figures 225–231 on Plate XVIII (from *Löhnis* and *Smith*, 1916 *a* and *b*) illustrate these various modes of formation of the symplasm, which may all occur with the same species, as shown here with *B. azotobacter*. That all types of vegetative cells, as well as of reproductive organs, are able to enter the symplastic stage is also demonstrated by these photographs.

Like the structure, the staining reaction of the symplasm can also show wide variations. In such cases where darkly staining membranes, especially those of regenerative bodies, participate in the process generally deeply staining flaky masses are produced, whereas the voluminous clumps, resulting especially from dissolved endospores or gonidia or from the agglomerated contents of large vegetative cells, are usually entirely unstainable by aqueous dyes. Frequently of course, large masses of symplasm are made up by both deeply staining and unstainable parts. *W. Winkler* (1899) reported to have directly observed the transformation of crumbly dark flakes into voluminous "plasmodia." Thus far I have not seen such changes; but the presence of very thick clusters of the peculiar bright slimy masses in old cultures rich in symplasm makes it, indeed, quite probable that special structural alterations may take place, which remain to be studied. *Letzerich* (1876), too, has reported that he observed directly a growth of bacterial "plasmodia" as such; the inner circle inserted within the large irregular symplasm in the lower left corner of the drawing reproduced as figure 80 on Plate R was explained by the author as indicating the original size from which the upgrowth started. It is impossible to decide at present whether or not this old report is to be accepted as correct.

The variations in the staining qualities of the symplasms make it easily to be understood why, for instance, the tuberculosis "zoogloea" was found by *Malassez* and *Vignal* (1884) to be not acid-fast and either not at all or with difficulty to be stained with aqueous dyes, while *Amrusch* (1886) recorded a slight acid-resistance. *Metchnikoff* (1888 *a*) saw the slimy amorphous masses assume a yellow color, when they were treated like the tubercle bacilli; and *Maher* (1910–1913) found again his tubercle "matrix" to be either not or slightly acid-fast. According to *Lutz* (1886) the "gloeal masses" of *B. leprae* are stainable with common aniline dyes, and turn bluish-red when treated with Gram's method, while they were seen by *Pernet* (1902) to vary in their staining qualities. Analogous results concerning the "plasmodia" of *B. radicicola* have been recorded by *Hiltner* (1898), and by *Bastian* (1905, p. 186) with his mixed cultures.

Iodine stains the symplasm either yellow or brown, like the hyalin and amyloid substances in the animal tissue, but this reaction may again vary, as has been shown by *Morck* (1891) with

B. radicicola. *Letzerich* (1874) saw sometimes, but not regularly, a blue color develop in his diphtheria "Plasmaballen" when they were treated with iodine and sulphuric acid.

Amoeboid movements of bacterial symplasms have been seen by *Letzerich* (1876), *Dowdeswell* (1889), *W. Winkler* (1899), and *Münden* (1907). *Dowdeswell's* observations, which were made with *V. cholerae*, have been refuted by *Friedrich* (1892), who asserts that they can not be accepted as correct. The German author admits, however (p. 104), that he also saw the bacilli dissolve into irregular flakes of plasma ("unregelmässige Plasmafetzen"). But that he did not see a new growth of bacilli arising from these flakes was very probably due to faulty experimenting. Internal, oscillating or gyrating movements have been noticed by *Perty* (1852), *Amrusch* (1886), and by *Frank* (1890). I have also seen this kind of movement in hyalin symplasm, whereas I have had no opportunity thus far to confirm the findings concerning amoeboid motility.

That the voluminous agglomerations of symplasm are endowed with a comparatively high resistance against the solving action of acids, alkali and hot water is a priori very probable. The prominent rôle which they have played in *Bastian's* experiments on "abiogenesis" and "heterogenesis" shows that they readily withstand long continued heating. *Metchnikoff* (1888 *a*) discovered that the symplasm of *B. tuberculosis* is very resistant against acid and alcohol. *W. Winkler* (1899) found out that by adding a 4–10 per cent solution of caustic alkali the symplastic masses present in thick bacterial growth become clearly visible, because they are less easily dissolved than the bacteria. And when I encountered for the first time what later turned out to be the symplasm of *B. azotobacter*, I also tried in vain to dissolve these doubtful clumps by treating them thoroughly with acid and with alkali. That they are sometimes hard to fix on the slide, by heating as well as by alcohol, has been mentioned above. This behavior, together with their heat resistance, will be considered in Chapter V, on account of their liability to cause faulty results.

That the increased resistance also protects the life within the symplasm to a considerable degree has been demonstrated by *Fuhrmann* (1908), who discovered that what he called the "detritus" of *Pseudomonas cerevisiae* remained alive for several months in a 10 per cent NaCl solution, wherein a young agar culture of the bacilli died within a very short time. If the symplasm encysts itself, as was observed by *Rosenbach* (1909), its resistance will evidently be still more increased, and at the same time its function as resting stage becomes quite obvious.

That this melting together of numerous cells and the ensuing thorough mixing of their ingredients are of great importance in regard to a better adaptation of the living substance to the environmental condition is especially clearly indicated by the very pronounced tendency of the liberated gonidia to enter first the symplastic stage, before reproducing new cells. As was discussed in the foregoing chapter, the gonidia grow up to new cells very readily while still connected with the parent cell, or if they have otherwise access to genuine plasma, like that in dead or dying cells of fungi and algae. But in other cases free gonidia have been rarely found to be inclined to act promptly as normal reproductive organs, when kept under ordinary laboratory conditions, whose rather unnatural character is beyond dispute. Dissolution of the gonidia has been mentioned in the early publications of *Perty* (1852) and of *Billroth* (1874), and the same fact has induced many other investigators to believe that also in this case dissolution means death, and no further investigation was thought to be necessary. *F. Cohn* (1870) as well as *Zopf* (1879) have noticed, however, that the microgonidia produced by Crenothrix, instead of germinating to new threads, as the macrogonidia always did, first agglomerated to a "zoogloea," which after a period of rest gave new vegetative growth. *Ewart* (1878 *a*) recorded analagous results with the "spores" (gonidia) of "*B. termo*" (*B. fluorescens*); only after having formed the "zoogloea" they were able to reproduce rods. And it is not improbable that the reason why *R. Koch* (1877), after having made his interesting first photograph of the "lateral spores" (gonidia and regenerative bodies) of *B. fluorescens*, which was reproduced as figure 109 on Plate X and discussed on page 92, never returned to this subject, has again been this mistaken dissolution of the small round bodies. Anthrax gonidia displayed the same

deceptive behavior, when first studied by *Fokker* (1881–1882), and also their rôle, as well as that of the gonidia of other parasitic bacteria, therefore, has often been overlooked.

Very conspicuous is the formation of symplasm when large gonidangia, containing numerous gonidia, break up, forming a small flake or clump of hyalin substance. *Dowdeswell* (1889–1890) has been probably the first who did not follow the generally observed easy rule to discard quickly all such "dead involution forms." He studied carefully the flocculent "débris," formed by the gonidangia of *V. cholerae,* and saw new curved bacilli develop from the minute granules inclosed within the plasma flakes, which also sometimes exhibited amoeboid movements. *Mafucci* (1892) obtained similar results with the club-shaped gonidangia of *B. tuberculosis,* though he only assumed that the deeply staining "granules" within the granular masses might act as "spores," without being in the possession of an accurate experimental basis, on which to found his belief. *Meyerhof* (1898), who worked with diphtheria bacilli, was more radical when he reported that the clubs within 8 days disintegrated—

in krümelige Produkte, die als abgestorben angesehen werden mussten.

No explanation was given why the author felt compelled to draw this conclusion without first studying the subject more closely. The latter was done by *Fuhrmann* (1906–1908), who was careful enough not to discard lightly what he also considered to be merely "detritus" of the club-shaped gonidangia of *Pseudomonas cerevisiae* and related organisms. Therefore, he secured the characteristic upgrowth from it, as was shown in the photograph reproduced as figure 238 on Plate XIX. Similar results have been recorded by *Růžička* (1908) with *B. anthracis* and by *Herzog* (1913) with *Microc. gonorrhoeae.*

Especially noteworthy is the symplastic stage with the filterable gonidia. Authors who have studied these smallest bodies more thoroughly have always encountered pale, slimy masses of variable staining reaction, wherein the minute granules often showed a comparatively conspicuous upgrowth. The small globular or dumb-bell-shaped cell inclusions, observed by *Bernhardt* (1911) in scarlet fever, were seen to be embedded within the cells in a plasmatic stratum of a peculiar "cloudy" structure, which took the stain sometimes weakly, in other cases, however, quite readily. On the other hand *Hoefer* (1911), who studied the same subject at the same time in the same laboratory, did not see the small bodies found by his colleague, but only homogeneous, hyalin clumps of different outlines, which later contained numerous smallest granules. He is inclined to believe that these formations represent another phase in the development of the cell inclusions, and both descriptions taken together fit indeed exactly the general character of the symplastic stage of the bacteria. Furthermore, the photograph made by *Mallory* and *Medlar* (1916) of the agglomerations of their *B. scarlatinae,* taken from the tonsils, which was reproduced as figure 248 on Plate XIX, also leaves no doubt about its being a typical picture of a clump of symplasm, just beginning to reproduce larger cells. The trachoma bodies were found by *Addario* (1912) to be equally embedded in a homogeneous substance, and the coccoid bodies, isolated by *Noguchi* and *Cohen* (1913) from the trachoma inclusions, again formed clumps of finely granular structure. The "clusters of very minute organisms of quite indeterminable morphology," discovered by *Hort* (1916 *a*) in meningitis filtrate, apparently have been very similar to the small clumps of symplasm, which were found in our cultures of the filterable gonidia of *B. fluorescens,* and of which one is shown in the dark field in figure 234 on Plate XVIII (reproduced from our first preliminary paper, original fig. 42). The filterable organism isolated by *Healy* and *Gott* (1916) from the tissues of cholera hogs is said to occur also "in very small clumps, showing many minute bright points"; the plasmatic mass was once more found to stain either deeply throughout or not at all. A paper by *Foster* (1917) upon the etiology of common colds is accompanied by a photograph (original fig. 3, Pl. 9) showing clearly the symplasm formed by the filterable gonidia just beginning to reproduce small globoid bodies. Very similar pictures from the poliomyelitis germ have been published by *Amoss* (1917, pls. 44 and 46), and that excellent photograph of the symplastic stage of the filterable *Bact. antityphosum* of *Almquist* (1917), reproduced as figure 247 on Plate XIX and discussed on p. 177, deserves to be studied once more in this connection.

(c) REPRODUCTION OF REGENERATIVE BODIES AND OF VEGETATIVE CELLS FROM THE SYMPLASM.

The highly interesting reconstruction of cells from the symplastic stage may proceed, like the formation of the endospores within the cells, along two slightly different lines. Either the agglomeration of the granular material and its consolidation to a new full-sized cell are most conspicuous, or at first one center of reorganization becomes clearly visible, from which the new cell evolves in a comparatively slow development. Undoubtedly the first mode of action is the more striking one, and it has, therefore, prominently attracted the attention of such early investigators as *Pineau, Perty, Bastian* and *Béchamp*, whose reports and drawings have been quoted and discussed on the foregoing pages (pp. 167–172). But the second possibility has been also admirably described as early as in 1876 by *Lankester*, whose very interesting description and drawings have been reprinted on page 170 and on Plate XVI (fig. 209). *W. Winkler* (1899), too, saw the separate centers of organization surround themselves with plasma and in this way grow up to new cells (see the literal quotation on p. 175).

According to my own observations both types of reproduction may be found with the same species. Stained preparates show invariably as the first step the reappearance of minute deeply staining granules, which are especially conspicuous in the hyalin type of symplasm; we have named them "regenerative units" (*Löhnis* and *Smith*, 1916 *a*, p. 680). When large cells are formed directly, several of these units will gather and surround themselves with the uniting membrane; in other cases one unit increases slowly in size and builds up the new cell. It is quite obvious that these regenerative units are nuclear in character, and the same diversity which is noticeable in the adult bacteria cell (see p. 109) becomes also evident in its embryonic stage. This parallelism extends still further. In those cases where only one deeply stained granule is visible within each new cell, this either stays there as such, or it spreads uniformly throughout its inclosure.

Our photographs reproduced as figures 253–264 on Plates XX and XXI illustrate these different modes of reconstruction, as far as this is possible by such pictures, which are necessarily more or less inferior to the real appearance of the objects under the microscope. Appearance, agglomeration, and upgrowth of the minute regenerative units are well discernible, and a comparison of figures 256 and 262 with most of the others demonstrates clearly how the cells sometimes instead of emerging slowly as separate units from and within the amorphous symplasm are directly and sharply cut out from their matrix, which in this way divides itself, much as certain protozoa do, into "schizonts" which only after separation assume again their typical cell form. As figure 256 demonstrates, new sporulating rods may come into existence as such, although at first of a queer tadpole shape, they display prominently their embryonic endospores, which usually reach their full development together with the newly born cells themselves. Another noteworthy peculiarity is the development of entirely pale bodies, which may multiply as such for a long time, always refusing to take the aqueous stain. They are visible in figures 259, 262, and 263; in the last case the transformation of the deeply stained hairy symplasm into these unstainable bodies is very conspicuous, while it is a little more difficult to discern the pale ovals within the stained cloudy agglomerations of figure 262. All three photographs were made from *B. fluorescens*, but other species exhibit sometimes an analogous behavior. Occasionally a deeply staining granule is visible within an irregular pale cell, or within each segment of a pale sheath of varying length, but, like in the case mentioned above, later disperses itself, giving the whole new form the normal staining reaction and undoubtedly otherwise taking part in the reconstruction of the cell. Figures 70 on Plate VI and 235 on Plate XVIII present such dotted pale threads of *B. azotobacter*, partially dissolved in the latter case by heating, and on page 177 we have already discussed the similar consolidation of slimy threads formed by *B. coli* and *typhi*. The photographs made by *Toenniessen* (1913) of *B. pneumoniae*, which were reproduced as figures 37–42 on Plate IV and which were explained by the author as being "mutants," make another interesting object for comparative studies. They all illustrate very clearly our preceding discussion of the reconstruction of normal cells from the symplasm. A photograph of *B. coli* published by *Kellerman* and *Scales* (1916), which was repro-

duced as figure 44 on Plate IV, furnishes another good example of new upgrowth from the symplastic stage. And a comparison of figures 99 on Plate IX (Corynebacterium, *E. de Negri*, 1916), 240 on Plate XIX (Erysipelothrix *Rosenbach*, 1909), 223 on Plate XVIII (*B. coli*, *Kellerman* and *Scales*, 1916), 247 on Plate XIX (*B. antityphosum*, *Almquist*, 1917), and 255 on Plate XX (*B. Azotobacter*, *Löhnis* and *Smith*, 1916 *b*), will indicate how a simultaneous upgrowth of the regenerative units to uniformly coccoid bodies may give rise to new forms, which in no way fit the time-honored definitions of the old form species.

This holds equally true in regard to the round regenerative bodies, whose vexatiously uniform appearance with the different species has been already discussed on page 134. If they grow up in pure culture from the symplasm, pictures like those reproduced as figures 156 on Plate XII, 219 on Plate XVIII, 244 on Plate XIX, 257 and 258 on Plate XX become visible under the microscope, leaving the investigator much in doubt as to what species they may belong.

Often, but not always, the new cells mature first at the outside of the hyalin agglomerations, and this may lead to a peculiar starlike arrangement, as has been photographed by *M. Jones* (1905) in the picture of a motile water organism (probably related to *B. radiobacter*), which was reproduced as figure 274 on Plate XXII. The author believes that this rosette formation is "apparently effected by a uniform grouping of the descendants of a single cell and is in no sense an agglutination phenomenon." But a study of the photograph in the light of my own observations upon the star formation of *B. radiobacter* make the explanation given at first more probable to me. *Beijerinck* and *Delden* (1902) found also the stars of the last-named species often, though not always, embedded in a thick slime. And *Winogradsky* (1888, p. 38) described quite similar "radiate colonies" of his Thiothrix, wherein the young threads are living together in clusters, developing from the same slimy basis. The analogous structure of the clusters of Actinomyces has been discussed on page 174.

Cladothrix, Crenothrix, and other trichobacteria have been so often described as entering a "zoogloea" stage and as growing out of slimy flakes, which frequently serve as a basis for the threads, by which they are anchored to the ground, that such pictures like figure 267 on Plate XXI, showing a young thread of our spore-forming "yellow bacillus No. 41" developing from the symplasm, must evoke considerable doubt whether the "common" bacteria may not also in this respect come much closer to the "higher" bacteria, if they are only allowed to exhibit their properties more fully than is usually granted to them. Our photograph shows that at the side of the broad basis of the thread some regenerative units are still growing up within the flake, and exactly similar round bodies have been also photographed by *Molisch* (1910, original fig. 8, Pl. II) in what he calls the "Haftscheibe" of iron bacteria. That *Meirowsky* (1914 *b*) obtained analogous results with other bacteria and that a description given by *Lachner-Sandoval* (1898) of young actinomyces threads fits our picture completely has been mentioned on pages 174 and 177. It may be added that the threads of *Leptothrix* within the human mouth exhibit the same morphological character, according to *Robin* (1853), *Miller* (1889), and *Beust* (1907).

That sometimes the outer part of the symplasm may solidify and inclose the newly developed cells like a cyst has been mentioned on page 181 as an interesting parallelism to the behavior of the Myxobacteriaceae. But it seems as if such "macrocysts" of the bacteria, as they may be called to distinguish them clearly from the microcysts discussed in Chapter II, are no regular occurrence and no species mark. *W. Winkler* (1899) and *Münden* (1907) have noticed them with *B. coli* and *diphtheriae*, where they have been missed by other authors, like *Kellerman* and *Scales* (1916) and *Almquist* (1917). The environmental conditions undoubtedly play a very important rôle in this case, although *Müller-Thurgau* (1908) perhaps went a little too far when he assumed that practically the action of tannic acid alone was to be made responsible for the formation of the interesting "bacteriocysts," which he discovered in wine. The parallelism to *Billroth's* Ascococcus (1874), *Babes'* Ascobacterium (1895), *Moreno's* Ascobacillus (1901), *Winogradsky's* Amoebobacter and Thiocystis (1888), as well as to the last-named author's zoogloea form of Nitrosomonas (1892), is so evident that the whole subject undoubtedly needs a more thorough study, which should also try to clear up the early findings of *Letzerich, G. A.*

Hansen and *Babes*. (See pp. 170 and 171). Peculiar pseudo-macrocysts seem to occur occasionally in the body; *J. Israël* (1878) encountered round bodies in decayed teeth wherein some "Leptothrix" was seen to develop, and *Arndt* (1880) reported that he found saliva corpuscles filled with spirochaets and that he also saw spirochaets coming out and entering these bodies.

That large clumps of symplasm may encapsulate themselves has been discovered by *Rosenbach* (1909); his photograph was reproduced as figure 242 on Plate XIX. But another photograph of *B. typhi*, published by *Almquist* (1917), which was reproduced as figure 243 on the same plate, makes it very probable that much of what represents itself as large yeast-like cells in the symplasm of many different species of bacteria is in reality such encysted lobes, made up of a deeply staining membrane and a hyalin content. In some cases the investigators have been able to branch off really yeast-like cultures, as, for instance, *E. de Negri* (1916) from her Corynebacteria, but in other cases no growth of these problematical forms could be secured, e. g., by *Maher* (1913) with *B. tuberculosis*. And after having become acquainted with *Rosenbach's* findings, it seems to me, indeed, very probable that as in *Almquist's* typhoid cultures so also those very large dark bodies visible in our photographs of Azotobacter symplasms, reproduced as figures 253 and 254 on Plate XX, are no genuine cells, but encysted lobes of the symplasm.

These bodies then would be closely related to other still more curious forms, which in our preliminary communications have been called "irregular regenerative bodies," and of which it was said on page 122 that probably "sclerotia" would be a more correct denomination for them, but that final action in this respect can not be taken at the present. The two photographs of *Bac. subtilis* and *fluorescens*, reproduced as figures 65 on Plate VI and 261 on Plate XX, may serve as illustrations. The extremely polymorphous "bacteroids" of *B. radicicola* are another well-known example. At least part of the queer spiny bodies developing from the symplasm of the micrococci also belong to this class; and the same holds true in regard to those irregular bodies of *B. cyanogenes*, pictured by *Neelsen* (1880), which were reproduced as figure 85 on Plate S, as well as to similar abnormal forms of *Streptoc. lactis*, found by *Burri* (1898) in Swiss cheese. That these bodies are nothing else than pieces of symplasm surrounded by a more or less solid, deeply staining membrane is quite obvious in many cases; and many of them merely persist for some time and then dissolve again into a more or less homogeneous mass. Others, however, are able to propagate as such, at least temporarily; those cultures of irregular Actinomyces-like rods characteristic for the micrococci belong in this class. The abnormal Streptococcus cultures of *Burri*, mentioned above, also grew as such for some time.

That as in these so also in other cases a close study of the development taking place within and from the symplasm is the best means to attack successfully many of the numerous problems concerning bacterial pleomorphism, variability, occurrence of so-called involution forms, limitation of the species, and similar points, needs no prolix discussion. It is equally obvious that chemical, physical, and biological reactions will often exert a much stronger influence when they are acting upon the symplasm than during the time the living material is standing against them in a rather stable organization within the cell. Undoubtedly, *Fokker* (1902–1903) went here, as in his heterogenetic speculations, too far when he assumed that by mixing various species of bacteria in their symplastic stage new species could be created at will, but he was perfectly right in making the following important statement (1903):

> Wo sich in einer indifferenten Flüssigkeit eine einzige Mikrobenart vorfindet, entstehen nach der Dissociation Mikroben der gleichen Beschaffenheit . . . Wo sich aber zwei oder mehrere Arten vorfinden und die dissociierten Plasmata sich vermischen, können sich aus diesem Gemisch Mikroben bilden, die die Eigenschaften der ursprünglich anwesenden in sich zu einer Einheit kombinieren, also von jeder der eingesäten einzelnen Arten verschieden sind. Auch ist die Möglichkeit nicht ausgeschlossen, dass bei der Dissociation in einer Nahrlösung, welche Bestandteile enthält, die in dem Substrate, in welchem die Mikroben erzogen sind, fehlten, diese Bestandteile auf das dissociierte Plasma einwirken, so dass letzteres Veränderungen erleidet, welche sich in den Eigenschaften der aus diesem Plasma regenerierten Mikroben kundgeben.

It is evident that the perplexing problems concerning the often so far-reaching morphological and physiological alterations of the bacteria caused by symbiosis, as well as by the change of substrate and environment, are becoming much more accessible, if the symplastic stage is

chosen as the starting point in such experiments. That a mixing of the symplasms of naturally related bacteria, like the streptococci and the diphtheroids, will lead to the appearance of interesting intermediate varieties, as mentioned on pages 40–41, is very well conceivable, just as well as or even better than the analogous facts caused by cross-breeding among the higher plants or animals. It is practically unavoidable that the reconstruction of new cells from such a mixed symplasm leads to the incorporation of elements of different parentage, so that the newly born variety (not species, as *Fokker* thought) will combine the characters of the original strains.

With the substrate it is quite similar, as *Fokker* has pointed out already. The upgrowth of the regenerative units within the symplasm is very similar to the development of bacterial gonidia within the dying or dead plasma of other plants or animals, which has been discussed on pages 148–150. That the natural varieties of the bacteria exhibit so often to such a marked degree the specific influence of their habitat is not astonishing, if one bears in mind how the very intimate contact between substrate and living matter in the symplastic stage must exert its direct influence upon the composition of the new cells.

It may be expected with certainty that renewed experiments on the effects of "cross-breeding" and adaptation of the bacteria will furnish results of great importance to bacteriology, as well as to biology generally, if they will be centered upon the symplastic stage in bacterial life. It can even not be denied that the rôle played by the regenerative units in the reconstruction of new cells from the symplasm displays many features, which remind us of the activities ascribed to the hypothetical "gemmules" of *Darwin* (1868, p. 448), the "plastidules" of *Haeckel* (1876), the "microplasts" of *Hanstein* (1882, p. 218), the "pangens" of *Vries* (1889), the "germplasm" of *Weismann* (1886, 1892), the "bioblasts" of *Altmann* (1894, p. 141), and the "physiological units" of *Spencer* (1898, p. 226). The greatest resemblance is noticeable in regard to *Spencer's* physiological units, which were declared to "possess the property of arranging themselves into the special structures of the organism to which they belong" and to be "complete aggregations of smaller chemical units, compounds of highly compound molecules." But also *Altmann's* hypotheses upon cell formation are bound to gain new interest when linked up with our new point of view. In regard to the higher organisms *Altmann* said (l. c., p. 8):

Die Zellen sind nicht Elementarorganismen, sondern Colonien von solchen mit eigenartigen Gesetzen der Colonisation; die Zellen entstehen aber nicht durch das Zusammentreten der Kügelchen, sondern sie sind daraus in jenen geschichtlichen Perioden entstanden, die den mikroskopischen Elementen gerade so eigen sind, wie den groben Formen der Lebewesen auch.

That the theory "omnis cellula e cellula" is not so generally applicable, as *Altmann* and many other authors believed, has been pointed out on page 167. But a study of the symplastic stage in the lives of the lower organisms proves conclusively that *Altmann's* opponents, like *Hueppe* (1896, p. 2), *A. Fischer* (1899, p. 295) and *A. Fischel* (1903), erred to a still greater extent when they disputed the fundamental importance of those "granules" for the life of the cell. One has only to behold their agglomeration or their growing up to new cells under the microscope, to become quickly convinced of their being, indeed, the "elementary organisms," forming temporarily a comparatively stable association in the form of a coccus, a rod, or a spirillum, but continuing their existence unimpaired after these cells have undergone renewed dissolution. The staining reaction of these granules may change within the symplasm, as it does within the cells, where this fact has caused so many differences of opinion among the various investigators. When, for instance, *Metzner* (1903) reports that the small granules in many animal cells take the fuchsin stain while young, but become unstainable when they grow old, and that in the latter stage they serve the metabolism of the cell, he is touching evidently the same fundamental fact which manifests itself in the development of the pale cells from agglomerations of well-stained regenerative units, as mentioned above, as well as in the variable behavior of the gonidia within the bacterial cell, as was discussed in Chapter II.

The physiological value of the symplastic stage for the bacterial life is very clearly indicated by the two facts, that the symplasm is formed from time to time in cultures kept for long

periods, but that it is also often produced by very young cultures immediately after they have been transplanted to a new substrate. *Buchanan* (1918) is of the opinion that the bacterial development proceeds regularly in seven phases, which are defined by mathematical formulas. However, his assumption that at the beginning always a "stationary" period and "lag" be noticeable, and that the "logarithmic phase of growth," the "phase of negative acceleration" and the "maximum stationary phase" be followed with mathematical certainty by the "accelerated death rate" and the "logarithmic death rate," is not in accordance with many well-established facts. When *Chesney* (1916) studied the so-called lag in the development of newly transplanted cultures, he noticed that no lag occurred when the transfers were made at the time of maximal growth, but that it was always exhibited by older material. However, not only old cultures, also young ones may show this "lag." When we transferred our Subtilis and Azotobacter cultures every morning and evening during several weeks, always from and to the same substrate (meat agar for Subtilis, mannite agar for Azotobacter), no lag was noticeable in the growth of the subcultures for several days, while it was very pronounced during the next days, then again immmediate upgrowth took place, again a period of lag followed, and so on. Microscopic examinations showed clearly that either the cells propagated as such, or that they first entered the symplastic stage, and it was especially these experiments which we accepted as evidence of the alternation between both modes of life (*Löhnis* and *Smith*, 1916 *a*, p. 679). That the same alternation takes place when cultures are kept for a longer period without being transferred to new substrates is indicated by the results obtained by *Riemer* (1909) and by *Springer* (1913), which have been quoted on page 28, and it is proven by our continued studies of all our 24 Azotobacter strains, which exhibited very distinctly in successive microscopic tests their persistent passing through the various phases of their life cycle, when kept permanently in the same solution (without any transfer) for more than a year. That under such conditions metabolic products and other external influences will act besides the internal causes, which were practically solely responsible for the results mentioned above, is not to be doubted. In nature, however, the situation is the same. And it will be advisable not to be too quick in declaring changes in form and function, often noticeable in old cultures, as being "merely" the result of "involution or degeneration," caused by the "detrimental effect of the metabolic products." It is true that secondary and tertiary colonies, growing on old agar slants, often abound in "abnormal" cells, but as these cells, according to *Preisz* (1904) and others, are usually more resistant than those which grew first, and the so-called involution forms, as was fully discussed in Chapter I, are often more numerous in young than in old cultures, it seems best to apply the newly won knowledge of the rôle played by the bacterial symplasm, to these facts and to make them the object of renewed and more thorough studies. Why *Fürst* (1914) found in the course of his experiments upon the variability of *Vibrio proteus* that in the 4-months-old cultures a period of rest preceded the return of the original type of growth, is easily to be understood, and it is equally obvious why apparently fully stabilized varieties, that have remained constant through hundreds of transfers made during several years, eventually may return to the original type. A close investigation upon the reproduction of the different types of cells from the symplasm will elucidate all such experiments to a very considerable degree.

That practically all of the symplasm is used up for the reconstruction of the new cells is an interesting sign of Nature's economy, which was first recorded by *W. Winkler* (1899), and which became again very conspicuous in many of our experiments. (See *Löhnis* and *Smith*, 1916 *a*, pp. 680 and 692, and the photographs reproduced as figs. 215, 216, 219, 220, 223, 243, 256–261, and 263 on Pl. XVIII–XXI.)

In an interesting paper upon autolysis, wherein the participation of assimilation and dissimilation in all vital processes is thoroughly discussed, *Nicolle* (1913, p. 446) makes the following statement, which is of special importance for our subject:

Lorsque l'assimilation et la désassimilation s'équilibrent harmonieusement, ... c'est la vie stationnaire . . . Quand la désassimilation l'emporte, mais que l'assimilation conserve une intensité suffisante, c'est l'atrophie. Lorsque la désassimilation l'emporte, tandis que l'assimilation tombe au-dessous d'une certaine valeur minime, c'est l'autolyse. Quand l'assimilation l'emporte, mais que la désassimilation conserve une intensité suffisante, c'est l'hypertrophie,

voire l'hyperplasie. Lorsque l'assimilation l'emporte, tandis que la désassimilation tombe au-dessous d'une certaine valeur minime, c'est l'autocoagulation, phénomène inverse de l'autolyse; c'est la naissance de formes résistantes, rigides, coagulées, condensées . . . Chose curieuse, les deux tendances opposées se partagent quelquefois la meme cellule (sporulation rapide, lors d'inanition brutale) donnant ainsi l'image d'une action et d'une réaction également excessives.

But in the same manner as the French proverb "Les extrêmes se touchent" is applicable to this latter case, it holds equally true in regard to many instances, where the new forms emerging from the symplastic stage are not, as might be expected at the first moment, normal vegetative cells, but, quite to the contrary, regenerative bodies, rods with endospores, and all kinds of "giant" forms, which are usually classed as signs of involution and degeneration, and which only in the course of their further development gradually resume that harmonious equilibrium between assimilation and dissimilation which, according to the French author, characterizes stationary life.

2. THE SYMPLASTIC STAGE IN THE DIFFERENT GROUPS OF BACTERIA.

That the so-called Ascococcus of *Billroth* (1874) does not represent a special genus, but is merely a type of growth of micrococci developing from the symplastic stage, is hardly to be doubted, despite an opposite statement made by *F. Cohn* (1875, p. 151). A drawing published by the latter author has been reproduced as figure 275 on Plate XXII (from original fig. 5 on Pl. V), where it may be compared with another picture (fig. 276), published by *Rabe* (1886, original fig. 2 on Pl. IV) of his *Micrococcus botryogenus*, which exhibited these actinomyces-like agglomerations only within the tissue, while on artificial substrates the development did not differ from that of any other Micrococcus.

A characteristic photograph of *Micrococcus candicans* growing up from the symplastic stage has been reproduced as figure 216 on Plate XVIII (from our second preliminary paper, 1916 *b*). All intermediate steps from the smallest regenerative units up to full grown cocci, like those shown in figure 1 on Plate I, are clearly discernible. The peculiar clusters of irregular, spiny, rodlike regenerative bodies, in figures 2 and 8 on Plate I, described in Chapter I as a characteristic type of growth of the micrococci, are equally the result of a complete transformation of flakes of symplasm of *Microc. candicans*.

Figure 264 on Plate XXI (taken from our second paper, 1916 *b*, original fig. 53) demonstrates the analogous behavior of a Sarcina. Again at the edge of a large flake of symplasm of *Sarcina flava* the gradual development of the regenerative units to large cells is to be seen. And in figures 16 and 17 on Plate II the final transformation of the large cells into normal sarcinae has been shown. Before having reached their definite shape, the packets are often connected by more or less solid bridges, which are clearly visible in figure 16, and which have been described before by *Sauerbeck* (1909) in a paper upon a *Sarcina mucosa*, of which several packets also frequently were seen to be enclosed in a slimy "capsule" (probably of symplasm).

The ability of staphylococci and gonococci to produce in 3–4 weeks old cultures "white pleomorphous clumps," similar to those of the so-called syphilis bacillus, as shown in figure 217 on Plate XVIII, has been mentioned already by *Niessen* (1898). But it was *Herzog* (1913) who first pointed out that this passing over of the gonococci into such "verquollene Schleimmassen" is of considerable etiologic importance, and that these clumps should not be lightly discarded as dead.

Analogous observations concerning streptococci were made by *Billroth* as early as in 1874, upon which he reported (p. 12):

> Das Plasma tritt in Form amorpher, körnig-schleimiger Substanz aus den Kugeln hervor . . . Ob damit das Pflänzchen abgestorben ist, will ich dahin gestelltsein lassen.

Why he did not succeed in getting a new development with these organisms, while in other cases he secured positive results with similar bacterial "plasmodia," must be left undecided. That it was undoubtedly the regenerative units and round regenerative bodies growing in and from the symplasm of lactic acid streptococci in milk which misled *Fokker* (1901) to his anachronistic hypothesis of the heterogenetic origin of milk bacteria from casein granules has

been discussed on page 172 and illustrated by figure 214 on Plate XVIII. Figure 215 on the same plate pictures, on the other hand, a flake of symplasm of the same species which, however, is transforming itself directly into normal vegetative cells of *Streptococcus lactis*. That as with other bacteria, so also with this species, the symplasm may break up occasionally into entirely irregularly shaped regenerative bodies may be concluded from an observation made by *Burri* (1898), who discovered in faulty Swiss cheese colonies of an organism, belonging into the group of *Bact. Guentheri* (*Streptoc. lactis*), which besides a few normal cells contained numerous irregularly curved and distorted forms, which, however, were able to multiply as such for some time, just as the analogous irregular regenerative bodies of the micrococci are inclined to do.

The findings of *Bernhardt* (1911), *Hoefer* (1911), and of *Mallory* and *Medlar* (1916) concerning the causative agent of scaralatina, which have been quoted on page 184, represent another important contribution to our knowledge of the symplastic stage in the life cycle of the streptococci. And it is very probable, too, that in the case of poliomyelitis analogous results will be reached. The photograph published by *Rosenow* and *Towne* (1916), which was reproduced as figure 9 on Plate I, looks much like a picture of symplasm producing new cells, and that various filterable vira have been found in close connection with such slimy, granular, differently staining masses, characteristic for this stage, was mentioned on page 185.

The small micrococci of about 0.15μ diameter, embedded in thick zoogloea masses, which *R. Koch* (1878) found instead of septicaemic bacilli in spreading abscesses in rabbits, and of which he discovered that even the unstainable homogeneous part proved to be infective (causing septicaemia), may well be accepted as the regenerative units of *B. septicaemiae; Koch's* drawing, reproduced as figure 211 on Plate XVII, indicates clearly that he had large agglomerations of symplasm under the microscope.

In the case of *B. radicicola* the symplasm and the various growth developing from it have been the cause of widely divergent conclusions reached by the different authors. As was mentioned on page 180, the organism has been placed among the Myxomycetes as well as among the Myxobacteria. *Frank* (1879) thought at first that the infective threads and the branched and budding forms developing from them should be accepted as mycelium and haustoria of a fungus. Later (1887), with the help of his pupils *Brunchorst* (1885) and *Tschirch* (1887), he deprived it entirely of its microbial nature; the "bacteroids" were now declared to be cell products of the legume. Two years later, however, after *Beijerinck* (1888) had isolated *B. radicicola*, *Frank* (1889) discovered that the infective threads be "plasmodia" of a peculiar "Rhizobium leguminosarum" and the "bacteroids" some kind of "mycoplasma." But in 1890 the German author also came to the conclusion that bacteria are to be made responsible for the various types of growth within the plant. *Moëller* (1885) also classed the alder organism at first among the Myxomycetes, because he saw the finely granulated plasma differentiate itself into round "spores," i. e., regenerative bodies, while he later (1890) assumed it to be a "unicellular hyphomyces" (*Frankia subtilis*), producing globular, oval, or pear-shaped "sporangia" of 4–6μ diameter at the end of the "hyphae," wherein "spores" are said to develop, which later reproduce a new "mycelium." The analogous change of opinion is also to be found in *Prażmowski's* (1888–1890) important papers upon the nodule organism of the leguminous plants. At first the "Knöllchenpilz" was described as forming large cysts, which after being placed in water liberated their content, made up of "bacteroids" embedded in a slimy, plasmatic substance. But later these cysts were accepted as being encapsulated colonies of bacteria. *Laurent* (1890) was inclined to place *B. radicicola* at the side of *Pasteuria ramosa* on account of the similarity noticeable between the "bacteroids" of the nodule organism and the branched clubs characteristic of *Metchnikoff's* organism. *Morck* (1891) found out that their regular bodies occurring in the root nodules of different legumes are either able to reproduce directly small motile bacteria or that they break up at first into round regenerative bodies. Their resistance against acid and alkali proved to be comparatively high. The granular plasma, visible in the youngest part of the nodules, was seen to produce either round or irregular forms or directly small rods. When studying the nodules of Alnus *Hiltner* (1898) obtained very similar results. Irregular slimy clumps and threads, containing rods, were seen, as well as "sporangia," produced by the rods or the threads,

which divided themselves into round "spores," which in their turn reproduced new rods. A later publication by *Hiltner* and *Störmer* (1903) contains those interesting photographs reproduced as figure 236 on Plate XVIII (from original fig. 8 on Pl. II), showing the "sporangia" of Alnus, and as figures 271 and 272 on Plate XXI (from original figs. 5 and 6, Pl. II), illustrating the analogous development of round bodies within the nodules of clover and pea, respectively. *Shibata* (1902) reported that the round bodies of Alnus may occasionally enter a process of multiple segmentation, similar to that sometimes observed with microcysts of streptococci and of other bacteria, which has been discussed on page 143. As figure 273 on Plate XXI a photograph has been reproduced (*Löhnis* and *Smith* 1916 *a*, original fig. 34), showing a flake of symplasm from a root nodule of red clover, which is producing clubbed and branched "bacteroids" as well as small, round regenerative bodies.

An excellent photograph of round regenerative bodies, found in cultures of *B. coli* by *Kellerman* and *Scales* (1916), has been reproduced as figure 44 on Plate IV. It should be compared with *Hiltner* and *Störmer's* Alnus picture (fig. 236 on Pl. XVIII). That also in this case the large bodies grew up from the symplasm is indicated by other details visible in the photograph. The hyphae-like threads of *B. coli*, shown by the first-named authors in two other pictures (figs. 45 and 224 on Pls. IV and XVIII), make interesting counterparts to the "infecting thread" of *B. radicicola*. In figure 223 on Plate XVIII the simultaneous and uniform upgrowth of the regenerative units of this species is equally well demonstrated. That the symplasm of *B. coli* may sometimes exhibit amoeboid movements has been observed by *W. Winkler* (1899) and by *Münden* (1899).

The picture published by *Almquist* (1916) of the various cell forms of *B. typhi*, which was reproduced as figure 243 on Plate XIX, shows very clearly the consolidation of the plastic substance into slimy threads and large globules. *Meirowsky's* (1914 *b*) drawings of what he calls "umbels" of paratyphoid and enteritis bacilli exemplify the upgrowth of new rods and threads from the symplasm. A few reproductions are to be found on Plate XIII (fig. 178, right lower corner) and on Plate XIV (second column).

That in cases of rhinosclerom the formation of symplasm by the causative agent is rather conspicuous has been indicated by the early findings of *Cornil* and *Alvarez* (1885) and of *Klebs* (1887).

A good illustration of the regeneration of new cells from the symplastic stage among the lactobacilli is given in the photograph of *B. acidi propionici c*, published by *Almquist* (1917) and reproduced as figure 246 on Plate XIX. The "vesicular forms" of *B. bifidus*, which *Tissier* (1900) considered to be degenerative, are probably, like similar forms frequently to be found with *B. radicicola, coli, pneumoniae, Azotobacter*, etc., another type of new cell formation from the symplasm. *Tissier's* drawing, which has been reproduced as figure 8 on Plate C (the "formes vésiculeuses" are to the right), should be compared with the photographs made by *Toenniessen* (1913) of *B. pneumoniae*, reproduced as figures 38–41 on Plate IV; the gradual development of regular cells from these irregular intermediate forms is especially well discernible in this case. Other data in regard to the symplastic stage of members of the *B. pneumoniae* group are given in a paper by *Jehle* (1902).

A *Bac. tubifex*, described by *E. Dale* (1912) as causative agent of a disease of potato leaves, was seen to produce infecting threads of the same appearance as those of the nodule bacteria, and probably also of the same physiological quality.

The important findings of *Rosenbach* (1909) concerning the symplastic stage of *B. erysipelatos suum* (*B. erysipeloides*) have been fully discussed on page 176. Highly interesting photographs of his paper were reproduced as figures 239–242 on Plate XIX, and as figures 27–29 on Plate III.

The mycelial upgrowth shown in the last-named picture invites comparison with a similar photograph made by *Rowland* (1914) of *B. pestis* (see fig. 30, Pl. III), while other data relating to the symplastic stage of this organism have been observed, but not correctly interpreted, by *N. K. Schultz* (1901, see figs. 218–221 on Plate XVIII and previous discussion on p. 176).

The agglomerations of growing regenerative units of the bacillus isolated by *P. Th. Müller* (1913) in cases of typhus exanthematicus, which have been reproduced as figure 22 on Plate II,

deserve to be compared with figures 216, 223, 240, 247, and 255 on Plates XVIII–XX, picturing the same phase in the life cycles of other bacteria (*M. candicans*, *B. coli*, *erysipeloides*, *anti-typhosum*, and *azotobacter*, respectively). In addition, figure 24 on Plate II clearly represents another type of upgrowth from the symplasm of *Müller's* organism; although a glance at the torn flakes of symplasm visible in the field leaves no doubt that a more carefully made preparation would have presented much better objects for comparative study.

In *Hauser's* first publication upon his Proteus (1885) the symplasm with its regenerative units and their development to new bacilli has been fairly well described.

Analogous observations with various Pseudomonas species were made by *Fuhrmann* (1906–1908). One of his photographs is to be found as figure 238 on Plate XIX. Various phases in the development of different cell forms of *B. fluorescens* from the symplastic stage have been reproduced as figures 259–263 on Plates XX–XXI (from our second paper, 1916 *b*, original figs. 8, 49–51, 63). The photograph shown as figure 265 furnishes another good illustration of how different the cells of "typically" short rods may appear under such conditions; the picture was made from an aerobic cellulose destroying organism, *Bact. acidulum*.

What *Omelianski* (1899) described as a new nitrite-forming organism should be studied again, as its photographic picture, reproduced as figure 268 on Plate XXI, makes it practically certain that merely a clump of round regenerative bodies has been seen, which grew up from the symplasm, such as is shown in figures 257 and 258 (Plate XX) from *B. azotobacter*, or in figure 219 (Pl. XVIII) from *B. pestis*. The two other photographs of Nitrosomonas, made by *Winogradsky* (1892) and reproduced as figures 269 and 270 on Plate XXI, are good illustrations of macrocyst formation. The presence of the large round cells within the "zoogloea" (fig. 270) strengthens our belief, expressed on page 135, that the so-called Nitrosccoccus of *Winogradsky* (shown in fig. 198 on Pl. XV) is nothing but a type of regenerative bodies of Nitrosomonas.

Not many data are available at present concerning the symplastic stage of spore-forming bacilli. That it plays an important rôle in the life history of *B. anthracis* has been repeatedly discussed by *Fokker* (1881–1882 and 1902). *Young* (1914) made a few remarks upon so-called sporoblasts, apparently being agglomerations of regenerative bodies growing up from the symplasm and developing to spore-forming rods. Our own preliminary studies upon the life cycles of *B. azotobacter* and related sporogenous bacilli, however, leave no doubt that also within this group of bacteria correct and complete results will not be reached until detailed investigations have been carried out in this direction. The photographs of *B. azotobacter* (figs. 70 on Pl. VI, 225–231 on Pl. XVIII, 250–258 on Pl. XX), of *B. subtilis* (figs. 65 on Pl. VI, 233 on Pl. XVIII), of *B. malabarensis* (fig. 266 on Pl. XXI) and of the "yellow bacillus No. 41" (fig. 267 on Pl. XXI) will suffice to indicate that very many interesting problems are awaiting adequate research.

That vibrios and spirilla also pass through the symplastic stage has first been noticed by *Finkler* and *Prior* (1884–1885) and by *Weibel* (1887). *Dowdeswell* (1889–1890), however, is to be credited with having made the first more thorough investigations upon this subject. "Cocci" embedded in amorphous masses have been also found by *Jorge* (1896) in cultures of a vibrio isolated from water, but their true character was not ascertained. *Almquist* (1916) got an interesting culture of fairly resistant regenerative bodies from a cholera culture, heated up to 60 C.; in figure 244 on Plate XIX the upgrowth of these round forms from the symplasm is very well illustrated. It is not improbable that *Hueppe* (1885) had similar objects under the microscope when he made the sketch of a "zoogloea" containing round bodies which is visible in the center of figure 49 on Plate M. *Albrecht* (1881) discovered in blood cultures of *Spirochaeta Obermeieri* irregular clumps of dark points, which permanently changed their form, and he also observed the formation of new spirochaets from them. The more recent findings, recorded by *Meirowsky* (1914 *b*) with various spirochaets and by *Leishman* (1918) with *Spirochaeta Duttoni*, are in perfect agreement with those early discoveries. On Plate XIV, in the lower part of the second column, some interesting drawings made by *Meirowsky* of spirochaets

growing up from the symplasm are to be seen. Figure 86 on Plate S should be compared with them.

With the Mycobacteria some more data are available. The early findings of *Letzerich* (1873–1876, cf. page 170) have, of course, not been obtained with pure cultures of diphtheria bacilli; nevertheless, they invite further investigation. That such macrocysts as have been seen by this author may be found, indeed, in pure cultures of *B. diphtheriae* has been made very probable by results recorded by *Münden* (1899). Formation of round regenerative bodies from amorphous masses in old diphtheria cultures, i. e. from the symplasm, has been noticed by *Spirig* (1903) and by *Balfour* (1911 *d*). A fairly good photograph of various cell forms of *B. diphtheriae*, developing from the symplastic stage, has been published by *Almquist* (1917); it is reproduced as figure 245 on Plate XIX. That the amorphous agglomerations present in old cultures of *B. xerosis* are equally able to produce a new growth has been ascertained by *P. Ernst* (1888). On the other hand, it was evidently not correct, when *Morse* (1912) maintained that only one group of pseudo-diphtheria bacilli (*B. hoagii*) be characterized by the fact that in old cultures the bacilli "fuse into poorly staining masses," whereas *B. xerosis* and *Hofmanni* are said not to exhibit such changes. The photograph made by *Mellon* (1917) of diphtheroids from the lung, reproduced as figure 249 on Plate XIX, furnishes additional evidence in this respect. The publications of *Niessen* (1898, 1908) upon his so-called syphilis bacillus contain several interesting data concerning the symplastic stage of diphtheroid organisms, of which, however, only very cautious use should be made, on account of the uncritical manner in which they have been gathered and reported.

That with leprosy the symplastic stage of its causative agent is of considerable frequency and importance may be seen from the publications of *G. A. Hansen* (1880–1882), *Babes* (1883, 1907), *Lutz* (1886), *Czaplewski* (1898), *Barranikow* (1900), *Pernet* (1902), and *Meirowsky* (1914 *b*).

Equally numerous are the observations upon finely granulated or entirely homogeneous "zoogloea" masses in tuberculosis and in cultures of *B. tuberculosis*. The contributions made in regard to this subject by *Klebs* (1883), *Babes* (1883), *Malassez* and *Vignal* (1883–1884), *Amrusch* (1886), *Schroen* (1886–1904), *Metchnikoff* (1888*a*), *Arrigo* (1900), *Meier* (1903), *Maher* (1910–1913), and *Meirowsky* (1914 *b*) have already touched many points, which should be thoroughly studied. Especially the work of *Schroen*, though rather incomplete in itself, is undoubtedly worthy to be taken up anew and carried out in a more satisfactory manner; the data collected with *B. radicicola*, and the peculiar behavior of this organism within the root nodules of leguminous and of other plants, reveal many striking resemblances to what has been described and pictured by *Schroen* concerning his "new phthisiogenic microbe." That this is no fungus, as was assumed by its discoverer, is beyond doubt, despite the incompleteness of the report. The thick slimy threads, accepted as mycelia, resemble very closely those produced by *B. radicicola* within the plant.

The granular mass, found by *Crookshank* (1896), *Mertens* (1903), and others in the center of many clusters of Actinomyces, is obviously an unchanged part of symplasm, and the description given by *Lachner-Sandoval* (1898, quoted on p. 174) concerning the development of young threads of Actinomyces from flakes of symplasm, could be accepted as pertaining at the same time to any other kind of rod-like bacterium. *Meirowsky's* drawings (see Pl. XIII, fig. 178, No. 57, and Pl. XIV, second column, "Paratyphus B") and our photograph of the spore-forming yellow bacillus No. 41 (fig. 267 on Pl. XXI) fit *Lachner's* description completely.

The development of new threads of Cladothrix from round gonidia (or regenerative bodies ?), which are embedded in a "zoogloea" (symplasm), has been illustrated by *Billet* (1890) in the upper part of the sketch reproduced as figure 70 on Plate P. That the microgonidia of Crenothrix often enter the symplastic stage before new threads are reproduced has been pointed out by *F. Cohn* (1870) and by *Zopf* (1879). And *Perty* wrote already in 1852 (p. 215) in regard to Gallionella ferruginea:

Nach der Zerstörung der Hüllen ballt sich der Inhalt, der mehr oder minder die Form von Körnchen annimmt, die von 1/1500''' bis zu unmessbarer Kleinheit vorkommen, in Haufen zusammen. Diese manchmal unregelmässigen Körnchen scheinen eben sowohl zur Vermehrung zu dienen, als die regelmässigen, innerhalb der Fäden erzeugten, kugligen oder elliptischen Sporen.

That the so-called "Haftscheibe," considered by *Molisch* (1910) to be quite characteristic for certain species of iron bacteria, may be also correctly classified as a remnant of the symplastic flake, which produced the thread, is hardly to be doubted. On the other hand, the statement made by *Winogradsky* (1888, p. 40) that *Zopf* had been wrong in attributing to Beggiatoa the ability to grow sometimes attached to the substrate, and that such sulphur bacteria be representatives of a special genus Thiothrix, will have to be reconsidered in the light of the new facts mentioned above. Evidently all rod- and thread-like bacilli are able to make use of their symplasm for attaching themselves to their substrates if the conditions under which they are living are favorable to such an arrangement.

3. CONCLUSIONS.

From the details discussed on pages 166–195 the following conclusions can be drawn concerning occurrence and formation of the symplasm and the regeneration of new cells from the symplastic stage:

(1) All bacteria live, in vivo as well as in vitro, alternately in an organized and in an amorphous stage. By the partial or complete dissolution of vegetative and reproductive cells a plasmatic mass, the symplasm, is formed, which after a period of rest and according to circumstances may transform itself into new cells of the same or of a more or less modified character. It has been found, for instance, in young as well as in old cultures of *Microc. gonorrhoeae, candicans*, and other species of Micrococcus; various streptococci; *Bact. pneumoniae, rhinoscleromatis, coli, typhi, paratyphi, enteritidis, pestis, septicaemiae, erysipelatos suum, proteus, bifidus*, and other lactobacilli; Nitrosomonas; *B. radicicola* and *fluorescens; Bac. anthracis, subtilis*, and *Azotobacter; Vibro cholerae* and *proteus;* various spirilla and spirochaets; *Corynebacterium diptheriae* and *pseudo-diphtheriae; Mycobact. tuberculosis* and *leprae;* different Actinomycetes and trichobacteria. Within the body the presence of bacterial symplasm has been recorded in cases of gonorrhoea, trachoma, variola. scarlatina, poliomyelitis, meningitis, endocarditis, septicaemia, rhinoscleroma, anthrax, pseudo-tuberculosis, tuberculosis, leprosy, malignous granulom, diptheria, actinomycosis, actinobacillosis, recurrens fever and syphilis. It participates in the formation of hyalin and amyloid substances within the body. Observations made by *Pineau* in 1845 and by *Perty* in 1852 have already indicated that all microscopic life starts from the symplastic stage, which, however, is not entirely absent in the cell life of the higher organisms. The earliest complete description of the symplastic stage of bacterial life has been published by *Lankester* in 1876. The so-called autolysis of bacteria is in part identical with the formation of the symplasm. The dissolution of the cells should not be considered synonymous with death of the living matter itself, and the regeneration of new cells from the symplastic stage is not to be accepted as heterogenesis, although this has been done by *Bastian, Fokker* and others.

(2) The formation of bacterial symplasm proceeds always in two phases: First, the cells agglomerate to smaller or larger clumps; second, a more or less complete dissolution of the cells takes place, resulting in a crumbly or slimy mass, assuming the shape of flakes, irregular clumps or regular spheroid bodies, and being sometimes endowed with amoeboid motility. The dissolution of the agglomerated cells leaves either the empty cell walls as shadows, but still clearly visible, in the field, or they, too, are disintegrated, forming a more or less homogenous symplasm of an either hairy, granular, or entirely amorphous, hyalin structure, of variable staining qualities, and of fairly high resistance against acids and alkali. The different types of symplasm may be found with the same species of bacteria; one type may pass into the other. Presence or absence of amoeboid motility is no species mark; the same holds true in regard to an occasional encystment of the symplasm. All kinds of vegetative cells as well as of reproductive organs of the bacteria are able to enter the symplastic stage. Irregular regenerative bodies, gonidangia, and liberated gonidia (including the filterable ones) are especially inclined to produce symplasm, and even endospores may do the same.

(3) The reconstruction of new cells from the bacterial symplasm follows various lines, according to internal as well as external conditions (quality of the symplasm, environment, and

technique). At first always regenerative units become visible, which either grow up separately to new cells, or of which several may agglomerate and surround themselves with a uniting membrane thus forming at once full-grown cells. Usually the reconstruction starts at the edge of the symplastic flakes or clumps, occasionally leading to a distinctly star-like grouping of the new cells; sometimes, however, the transformation takes place simultaneously throughout the whole mass. The new cells formed are as a rule regenerative bodies of round or irregular shape, but normal vegetative cells may be also produced immediately. Endospores, too, may develop at once within the new cells. A uniform appearance is rather rare among the newly constructed cells; usually they are more or less pleomorphic. A special type of growth sometimes to be found in such cultures are broad, slimy threads, often of irregular outline, which by contraction or by segmentation reproduce normal vegetative cells. Like other irregular regenerative bodies they have been improperly classed as "involution forms." Generally all of the symplasm is transformed into new cells; occasionally, however, the outer part of it becomes membraneous and incloses the whole colony of newly developed cells as a "macrocyst," or a small flake of symplasm remains at the basis of a newly formed thread, fixing it to its substrate. All the different possibilities mentioned may be found with the same species of bacteria. Macrocysts have been seen with micrococci (Ascococcus), *B. radicicola,* Nitrosomonas, Ascobacterium, Ascobacillus, *Mycobact. leprae,* and with various sulphur bacteria (Amoebobacter, Thiocystis, Clathrocystis, and *Bacterium rubescens*); they indicate a closer relationship between *Bacteriaceae* and *Myxobacteriaceae.*

(4) As the various subcycles within the life cycles of the bacteria are connected by the symplastic stage, a thorough study of the regeneration of the new cells from the symplasm is essential for securing a correct knowledge of the principles governing the pleomorphism and the variability of the bacteria. Biological, physical, and chemical factors exert usually their most pronounced influence during this phase of the life cycles of the bacteria, which in their turn are at this time in a much better position to adapt themselves to changed environmental conditions, than they are during their cellular life.

IV. CONJUNCTION.

Our studies upon the life cycles of the bacteria led us to the conclusion (*Löhnis* and *Smith*, 1916 *a*, p. 700) that besides the formation of the symplasm another mode of interaction between the plasmatic substances in bacteria cells is generally to be found, consisting of the direct union of two or more individual cells. We called this process "conjunction," because frequently more than two cells are united, and a connecting bridge (yoke) is sometimes, but not always, visible; therefore, the terms "copulation" and "conjugation" are not well applicable.

Conjunct cells were constantly seen in cultures two to four days old. The conjunction always preceded the formation of the gonidia, of lateral and terminal regenerative bodies, as well as of exo- and endospores. The latter, too, sometimes entered the conjunct stage.

The formation of connecting bridges, first seen with large Azotobacter cells, reminded me of a similar observation made occasionally by *Förster* (1892), who found that in freshly collected living material of Chromatium Okenii, during the first 3 days, often a "primitive copulation" was noticeable, characterized by the formation of cylindric unstained bridges, leading from and to the unstained inner part of 2, 3, or more neighboring cells. Sometimes a knoblike inflation became visible in the middle of the bridge, and it was also no rare occurrence that only a half bridge was protruding from a single cell. No conspicuous change was seen to follow the act of "copulation," but the cells were especially large at this time, while they later lost in size as well as in vitality.

This, however, was the only confirmative finding which we could cite in our first preliminary report (1916 *a*, p. 687), though we pointed out in addition that conjunction of the bacteria, like their budding and the formation of the symplasm, has not only been seen by many bacteriologists, but also has been unknowingly reproduced in several illustrations in our daily used textbooks.

As figures 278–294 on Plates XXII and XXIII pictures are given, which may illustrate the appearance of various species in the conjunct stage. Figure 278 has been taken from *Förster's* paper. It makes a good counterpart to our Azotobacter photographs, No. 279–283. Figure 284 presents spores of Azotobacter in conjunction; the fine bridges are clearly noticeable also at some isolated spores. Figure 285 shows *B. fluorescens*, figures 286 and 287 *B. subtilis*. Figure 288 is a photograph of *B. Chauvoei*, made by *Itzerott* and *Niemann* (1895, original figure 48); figure 289 was taken from a contact preparate of a colony of *B. fluorescens*, made by *Axelrad* (1903, original figure 22); figure 290 shows *Bact. esterificans Stralauense*, photographed by *Maassen* (1899, original figure IX, 1); figure 291 was made by *Guenther* (1906, original figure 8) from a colony of large bacilli, isolated from a straw infusion; figures 292 and 293 are parts of a picture of the hay bacillus, published in the textbook of *Hiss* and *Zinsser* (1914, original figure 125); and figure 294 is another Azotobacter photograph, made by *Walton* (1915, original figure II, 8). By a careful examination of these pictures the various modes of uniting, which often replace the bridges between the cells, will be easily discovered. Especially a peculiar beak-like development of an end of a cell, stretching out to the side of another cell, is very striking. Sharp bents of the rods are equally conspicuous, as are the T and V formations, while little swellings or small droplets, sometimes noticeable at the touching points, will reveal their presence upon close scrutiny.

It goes without saying that the process itself is much better to be studied with the living material, and reproductions from stained preparates can only convey a more or less incomplete impression. But good photographs of living cells showing conjunction are hardly obtainable, and as with the symplastic stage, again direct microscopic studies are indispensable for reaching a correct view of the subject.

In his textbook on bacteriology *A. Fischer* (1903, p. 42) states very distinctly:

Geschlechtliche Fortpflanzung ist bei den Bakterien noch niemals, auch nicht andeutungsweise beobachtet worden.

That he did not know, at least, *Förster's* paper, which was published in the "Centralblatt für Bacteriologie," makes it very doubtful whether he was entitled to make such a strict statement. Numerous other observations, to be recorded on the following pages, are equally in open conflict with *Fischer's* attitude as well as with the standpoint taken by many other writers.

It was pointed out in the foregoing chapters that *R. Koch*, *Gaffky*, *Flügge*, and *Fraenkel* were undoubtedly wrong, when they established their rigid monomorphistic doctrine, that *Brefeld* as well as *Migula* were not in accordance with well-established facts when they asserted the occurrence of various types of reproductive organs among the bacteria to be a priori impossible, and that it was a serious mistake when *R. Koch* and *Loeffler* lightly discarded all that was already known at their time upon the symplastic stage of the bacteria. But these erroneous views are still upheld in many bacteriological textbooks, despite the very numerous facts which conclusively prove their inaccuracy. Concerning the occurrence of sexual processes among the bacteria much less data are available, but they are numerous enough and of sufficient weight to recommend the adoption of a more correct view than that held by *A. Fischer.*

It is to be readily admitted that for the practical bacteriologist a knowledge of the occurrence of sexual processes among the bacteria is of much less importance than a thorough acquaintanceship with their pleomorphism, their various modes of reproduction, and with their alternating between cell life and symplastic stage. This, however, does in nowise interfere with the great scientific interest of the subject.

Before taking up the data collected from the bacteriological literature, it seems advisable to discuss briefly a few points, which will be helpful for securing a better understanding and a more correct valuation of what has been done thus far by bacteriologists.

It has been emphasized already by *Darwin* (1868, pp. 431, 432) that sexual reproduction is not so very different from asexual reproduction, and that it is an error to assume that a bud differs essentially from a fertilized germ, though undoubtedly "beings produced sexually are much more liable to vary than those produced asexually." According to *Spencer* (1898, p. 265) the terms asexual and sexual multiplication are equivalent to cell reproduction and cell generation. *Delage* (1895, p. 117) makes the following statement:

Le conjugaison est bien véritablement l'intermédiaire entre la reproduction asexuelle par spores et la reproduction sexuelle par oeufs et spermatozoïdes . . . La conjugaison va nous présenter une série de formes qui par une extrémité confinent à la reproduction asexuelle, . . . et par l'autre passent à la reproduction sexuelle.

Sachs (1875, p. 203) distinguished between asexual generation, with asexual reproductive cells, developed independently without foreign aid, and sexual generation, i. e., development of new cells with the aid of another cell. If in the latter case the uniting cells are uniform, the process was called conjugation, if they are conspicuously different, fertilization.

Kruse (1896 *b*, p. 83) says:

Partielle Konjugation heisst der bei Infusorien weit verbreitete Vorgang, bei dem sich gleichartige Individuen vorübergehend mit einem Teile ihres Körpers vereinigen, je einen ihrer Mikronuclei mit einander austauschen und sich wieder von einander trennen. Ausstossung von Richtungsspindeln, Kern-Auflösung und -Neubildung findet dabei nicht statt.

It is obvious that this definition fits very closely to that type of conjunction which is most frequently exhibited by the bacteria.

According to *Prowazek* (1907 *b*) sexuality is an elementary process inherent to the living matter and either already discovered or expected to be found with all lower plants and animals. *Doflein* (1909, p. 158) states that as far as the protozoa have been studied multiplication by segmentation can not go on indefinitely, and that sometimes after a few, in other cases after thousands, of purely vegetative generations sexual processes are taking place, either in the form of copulation (i. e., complete uniting of two cells) or as conjugation (i. e., interaction between the nuclear substances of various cells).

With special reference to sexual processes among protists *Hartmann* (1909) has pointed out that fertilization is characterized more by the copulation of the cell nuclei than by the interaction of the cells themselves, and that, therefore, besides "amphimixis" between different cells, "automixis," i. e., the copulation of various nuclei within the same cell, should be taken under consideration as an important mode of fertilization among protists. A copulation taking place between sister cells is called "pedogamy," and declared to be frequent among amoebae, bacilli, and lower algae. Long-continued vegetative reproduction is accepted as causing a gradual increase in differentiation among the cells and their nuclei, and therefore the fertilization is viewed as a means of reestablishing the inner equilibrium, and thereby stimulating anew vegetative growth and multiplication. The effect exerted by amphimixis upon the variability of lower organisms has been discussed by *Pringsheim* (1910, pp. 120–126).

Of special interest are the following sentences, written by *Barker* (1901) in his first paper on Zygosaccharomyces, whose mode of conjugation is duplicated in a striking manner by the behavior of the large bacilli in their conjunct stage. The yeast cells, obtained from commercial ginger, produced beaks which touched each other with their tips, causing a fusion of the cells:

> The appearance of the compound cells, thus formed, was that of two ordinary cells attached to one another by an elongated neck with complete communication of their cavities through the neck, and at this stage with protoplasm filling up the whole of the cells and the neck.

A few hours later the formation of bright granules and of spores in both cells became noticeable. Sometimes the tubes did not conjugate, but turned into buds or branches. Satisfactory results concerning the behavior of the nuclei were not obtainable, but the author is inclined to accept the process as a sexual one, not merely as a fusion of cells, and he continues:

> There is one aspect of all simple sexual acts that appears worthy of further attention, and which is suggested very definitely by the present case. It would appear that whenever nucleated spore-producing protoplasm is being stored in neighboring cells, or whenever it has been accumulated and is parted by a septum, a strong tendency exists for union. Numerous examples can be given, such as the fusion of sporidia of Ustilagineae or of Protomyces, the nuclear fusions in teleutospores, aecidiospores, etc., or those in the ascogenous cells of Erysipheae, Exoascus, Peziza, etc., and in the basidia of Hymenomycetes, also the fusion of sister cells in some Conjugatae, e. g., Spirogyra.

Many additional data concerning the copulation of yeasts have been secured by *Guilliermond* (1910*b*—1912), who found the process rather widespread among the spore-forming yeasts and Schizosaccharomycetes; spores, too, sometimes showed fusion, occasionally already while still within the ascus. But numerous cells produced spores without previous copulation. Colonies of *Debaryomyces globosus* exhibited clearly the copulation occurring between sister cells. Often the two cells were quite different in appearance, "mais on ne saurait voir dans cette inégalité l'indice d'une tendance a l'hétérogamie." Other species, however, especially a *Zygosccharomyces Chevalieri,* furnished good examples of true heterogamic copulation; the whole content of a smaller cell (microgamet) passes over into a larger one (macrogamet), which transforms itself into an ascus.

According to *Marchand* (1912) the copulation of the spores by making beaks and bridges is fairly frequent with yeasts, though a great number of them germinate and develop independently.

That many parallels are presenting themselves between these observations and those enumerated above, relating to the behavior of the bacteria, is hardly to be denied. And this will become more evident when the following findings are also taken under consideration.

As early as in 1872 *Rindfleisch* pointed out that he often saw two bacteria united with each other, and that this union was not the result of fission. In 1875 *Klebs* reported in his V. contribution "Zur Kenntnis der pathogenen Schistomyceten" that motile rods often at first have the shape of short coccoid or oval bodies, and that these, after repeated touching and separating, at last enter a permanent conjunction, and then grow up into long rods and threads, which later segment themselves again into round cells. He calls the process explicitly "einen Act der Verschmelzung oder der Copulation."

Still more important is the following discovery, published by *Albrecht* in 1881. The cells of *Spirochaeta Obermeieri* were seen, when kept in blood at 37° C., to touch each other first with

their ends and then fuse together more or less completely, so that they presented the appearance of one organism. After a shorter or longer interval they separated again; but the author emphasizes that a true fusion is characteristic for this occurrence, which should not be mistaken for a casual apposition of two cells.

Buchner (1882) declared the occurrence of rods in V form to be characteristic of *B. subtilis*, while it was pointed out by *Escherich* (1894) that the long forms of the diphtheria bacillus are often to be found in V form or in rosettes, and that the ends touching each other are often broader than the rods themselves. *Kurth* (1898) and others have obtained analogous results with this species. Upon the behavior of the so-called *Vibrio denitrificans*, *Severin* (1897, p. 512) reported as follows:

In 1–2 tägigen Bouillonkulturen kann man häufig Stäbchen beobachten, die in sehr verschiedenartiger Vereinigung miteinander verbunden sind, bald zu zwei, bald zu drei, zuweilen noch mehr, bald in form von T, bald legt sich das eine Stäbchen an ein anderes in form eines Zweiges an, oder es vereinigen sich zwei derselben mit ihren Enden.

Under the title "An unusual bacterialg rouping" *Hefferan* (1912) discussed the various modes of rosette formation, as found by her with *B. rosaceus metalloides*. She is inclined to connect it with a peculiar mode of cell division, but the experimental support furnished for this assumption can hardly be accepted as convincing. The author herself explicitly admits that—

there remain numerous possibilities, yet untouched by investigation, as to the actual cause of this peculiar phenomenon, which I am inclined to believe is a problem closely related to the vital processes of the organism.

It was also noticed that not infrequently rods were swarming together to angles or to a rosette-like position, and that they then were either staying or again swarming away; "a peculiar clear space at the center" became often visible in this case.

One of our photographs of *B. radiobacter* (*Löhnis*) and *Smith*, 1916 *b*, original fig. 29) illustrating this mode of star formation has been reproduced as figure 277 on Plate XXII. A comparison with figure 274 on the same plate, showing the star formation from the symplasm, will be helpful for accurately distinguishing between both processes.

Apposition of motile cells in a T position to other cells has been further recorded by *Bajardi* (1902, with *V. lingualis*), who being evidently not acquainted with the analogous findings published before, wrote upon this fact:

Man findet hier die eigentümliche Erscheinung, dass häufig kürzere Stäbchen oder Fadenstücke sich rechtwinklig an die längeren Fäden anlegen, woraus man den Eindruck einer seitlichen Knospung gewinnen könnte.

Cytological investigations led *Rayman* and *Kruis* (1904) to the belief that copulation between young bacterial cells is by no means infrequent. And results obtained in ultramicroscopic studies induced *Gaidukov* (1906) to make an analogous statement.

Obviously without knowledge of *Albrecht's* early work, the conjunction shown by spirochaets has been repeatedly discussed during the last 10 years, and several authors have declared themselves to be inclined to interpret this process, whose last phase was often mistaken for longitudinal fission, as genuine copulation. See, for instance, *Sobernheim* (1907, p. 582), *Breinl* (1907), *Schellack* (1907), *Meirowsky* (1914 *b*), and *F. Levy* (1916). Especially the last-named author's dark field studies, made with *Spirochaeta Obermeieri*, are in complete agreement with those findings recorded by *Albrecht* 35 years before.

When studying the development of bacterial colonies *Graham-Smith* (1910) found that always a characteristic "post-fission movement" was noticeable, such as had been discovered by *Hill* (1902 *a*) with *B. diphtheriae*, indicating a decided tendency of the newly formed rods to place themselves parallel each other. This was realized either by "loop forming" (seen with *B. anthracis*), by "folding" (bacilli related to Anthrax, and *B. pestis*), by "snapping" (*B. diphtheriae*) or by slipping (*B. coli, pneumoniae, pyocyaneus, pseudo-tuberculosis, subtilis,* various vibrios and spirilla). The physiological meaning of this parallel arrangement has not been considered by the author; it seems, however, as if in well-made contact preparates of bacterial colonies always numerous cells are to be found in the characteristic conjunct stage, being connected by bridges or by beaks, such as are visible in figures 279–283, and especially in figures 289 and 291.

According to some observations made by *Faber* (1912) with *B. rubiacearum* pairs of rods in parallel arrangement may turn themselves by double folding into a cross-like position. This occurrence is similar to that described by *Hefferan.*

That the various modes of conjunction may be followed by the formation of lateral and of terminal regenerative bodies has been noticed by several authors.

Some of the drawings made by *Hueppe* (1885) of what he called arthrospore formation of *V. cholerae* (see fig. 49 on Pl. M) leave hardly any doubt that it is more correct to assume that the long spirilla in the characteristic V position, which later produce the round bodies at their ends, were in conjunction, than to accept this as a prefission phase. Similarly, *Babes* (1889) pointed out that the round regenerative bodies frequently seen by him with spirilla and vibrios are either located at one end of the cell or at the point where two cells touched each other, or, as he thinks, were they divided. The photograph of *V. cholerae,* made by *Friedrich* (1892) and reproduced as figure 140 on Plate XI, demonstrates especially clearly the appearance of conjunct cells and their relation to the formation of regenerative bodies.

The sexual processes ascribed by *Vincentini* (1893) to his so-called *Leptothrix racemosa* are probably to be interpreted as an example of conjunction, resulting in the production of round regenerative bodies. But the short abstract of the apparently rather confused paper, which was only accessible to me, allows no definite conclusion.

The very interesting drawings of regenerative bodies produced by acetic acid bacteria in 2-days-old cultures, made by *Henneberg* (1898) and reproduced as figure 57 on Plate N, represent the first clear indication that the formation of this type of bacterial reproductive organs is, indeed, very much alike to the zygospore- or to the ascus-formation of certain fungi. For instance, a picture of *Eremascus fertilis* published by *Guilliermond* (1910*b*) could be readily mistaken for a drawing of conjunct lactobacilli producing a lateral round regenerative body; even the septa visible within the mycelium find their counterparts in *Henneberg's* sketch. The following remark made by *Guilliermond* fits both cases equally well:

L'anastomose s'accompagne d'une résorption de la parois séparatrice des deux articles réunis et permet la mélange de leur contenu dans la cellule mère de l'asque.

A photograph made by *Maassen* (1899) of his *Bact. esterificans Stralauense,* reproduced as figure 290 on Plate XXIII, exhibits, besides other interesting details, in the middle of its upper edge an exceptionally good example of the initial step leading to the formation of a lateral regenerative body, which should be compared with the upper part of *Henneberg's* drawing. *Tissier* (1900) found the ends of his *B. bifidus* often inflated, especially those connecting two united rods; and at this junction frequently a round regenerative body ("une boule") became visible. Analogous observations were made by *Fuhrmann* (1906) with 2-days-old cultures of his *Pseudomonas cerevisiae.* Rods with terminal inflations were seen to touch each other sideways, and a connecting bridge was found to exist between these bulbs. *Fuhrmann* says:

Diese ganze Erscheinung erinnert sehr lebhaft an Bilder, wie wir sie bei der Zygosporenbildung zu sehen gewohnt sind.

Droba (1901) reported that he discovered "Zygo- and stylospores" with *Bac. tuberculosis,* and *Mühlens* and *Hartmann* (1906) thought that the round bodies which they found with spirochaets might be the products of some preceding act of fertilization. Some drawings made by *Prowazek* (1906*a*), reproduced as figure 89 on Plate S (from original figs. 10 *c*, 11*a* and *b* on Pl. II), illustrate very clearly how two separate regenerative bodies or one compound body (of the character of a zygospore) may be formed by two conjunct cells of *Spirochaeta gallinarum,* very much as it was seen and drawn by *Hueppe* (with *V. cholerae*) and by *Henneberg* (with *Bact. oxydans*). *White* and *Avery* (1909) noticed also quite correctly that the oval or kidney-shaped "nodules" of lactobacilli are located either at the point where two bacteria touched each other, or that each of them is supported by a short stem, branching out of the side of a rod. It was, however, far from being correct when they asserted:

Their formation may undoubtedly be considered a true plasmolysis.

The photograph of *B. subtilis,* published in *Hiss* and *Zinsser's* textbook (1914, original fig. 125), which contains those cells in the characteristic conjunct position, which were reproduced

in figures 292 and 293 on Plate XXIII, also presents at the same time a well-developed lateral regenerative body, visible in figure 150 on Plate XI. A photograph of *B. coli*, made by *Kellerman* and *Scales* (1916), which was shown as figure 185 on Plate XV, is of still greater interest. With most cells the conjunction is easily noticeable, and a pair in V position in the upper part of the field shows again the regenerative body being formed at the touching point. *Almquist's* pictures (especially figs. 135, 138, and 139 on Pl. XI) offer some additional confirmative data, relating to *B. typhi* and *V. cholerae*, as does figure 172 on Plate XII (a reproduction of one of our photographs of *B. bulgaricus*).

The formation of endospores has been connected with copulation, probably for the first time, by *Hueppe* (1891, p. 29), who wrote:

Die Endosporenbildung erscheint mir als wirkliche Fruktifikation, als einfachste Form einer Art geschlechtlicher Fortpflanzung, der Copulation, zur besseren Anpassung an die Art bedrohenden Aussenbedingungen.

This view was shared by *Gamaleia* (1900, p. 23); and on account of cytological results obtained with the large new species *B. Buetschlii* and *sporonema*, *Schaudinn* (1902) promoted the theory that the endospores represent the result of autogamy between neighbored cells, a theory which later has been confirmed by *Růžička* (1910), but contested by *Dobell* (1909–1911) and by *Swellengrebel* (1913). Investigations carried out by *Baur* (1905) upon the formation of arthrospores (or microcysts?) by Myxococcus led to results which are in several directions similar to those of *Schaudinn*, and the same holds true with regard to observations recorded by *Gross* (1913) concerning the arthrospore formation of spirochaets. *Park* and *Williams* (1914, p. 38), too, are inclined to interpret as "a primitive sexual process, a sort of autogamy" the fusion of metachromatic granules, which was seen to precede cell fission in the large, often branched, cells of diphtheria bacilli.

Another mode of interaction between separate bacterial cells has been described by *Vuillemin* (1888) in his studies upon the "zoospores" of the nodule organism from the leguminous plants as follows:

Parfois les zoospores se rapprochent et restent appliquées l'une à l'autre par le bout pointu . . . Les boules brillantes sont souvent placées sur les faces opposées. Nous ne savons trop quelle interprétation attribuer à cette sorte de conjugaison. A un certain moment il y a, semble-t-il, une soudure véritable sans que le corps des conjoints subisse des modifications visbles.

After separation one body was seen to move rapidly away, while the other became immotile, increased in size and turned over into what seems to have been a gonidangium or a large round regenerative body. The French author concludes (l. c., p. 193):

On se demande s'il n'y a pas là une sorte de fécondation, dont le resultat est de transformer la zoospore en spore.

Like *Vuillemin*, but apparently without knowledge of this author's findings, *Hartleb* (1900) was inclined to believe that the copulation of the "zoospores" of *B. radicicola* leads to the production of "zygospores."

That also a distinct sexual dimorphism may be found sometimes among the bacteria has been discussed for the first time by *Haberkorn* (1882), though it is not to be denied that his report does not look very trustworthy. Small bodies were seen to fuse with larger ones, which later developed to gonidangia (called "Samenkapseln" by *Haberkorn*). Essentially the same fact has been recorded by *Ferrán* (1885) in regard to the cholera vibrio. Small bodies, termed "antheridia," were seen to fertilize larger round "oogones," which afterwards became gonidangia. The Spanish author, who was hardly acquainted with *Haberkorn's* short communication in the "Botanische Centralblatt," points out that he found similar "oospheres" also with several bacilli. But his results differed in many respects so widely from those of *R. Koch* and his pupils, which then were accepted everywhere as the only reliable ones, that they probably would have been passed practically unnoticed, also if they had not been mixed with several quite unwarranted hypotheses, which were bound to create considerable distrust in *Ferrán's* whole work (cf. our discussion of his publication on p. 69). *Dowdeswell* (1889–1890), however, has fully confirmed *Ferrán's* discovery. Observations of the cholera organism in Ranvier's moist chamber showed him that, indeed, large round "oospores" are fertilized by small pear-shaped "zoospores," and that they afterwards break up into "sporules."

Firtsch (1888), on the other hand, who also paid attention to the large globules produced by *Vibrio proteus,* is of the opinion that they are simply the result of a fusion of the loops, frequently formed by the curved cells especially during the second day; despite the complete absence of thorough investigations in this direction, he feels justified to state:

Mit Fruktifikation haben diese Gebilde . . . natürlich nicht das Geringste zu tun.

Sexual dimorphism among spirochaets has been repeatedly discussed by protozoologists. For instance, *Perrin* (1906) interpreted the conjunction of thinner and thicker cells of *Spirochaeta Balbianii* as "conjugation of male and female gametes." *Prowazek* (1907 a), *Krzysztalowicz* and *Siedlecki* (1908), *Gonder* (1909), and others have shared this view, while it has been refuted by *Fantham* (1908), *Doflein* (1909, p. 315), *Dobell* (1912), and others.

A process of fertilization, very much like that described by *Ferrán* and *Dowdeswell* with *V. cholerae,* has been reported by *McDonagh* (1912) with *Spirochaeta pallida.* A round "macrogamete" was seen to be fertilized by a "microgamete," showing the typical form of a spirochaete, and afterwards to develop to a "zygote," which at first divided into four "sporoblasts" and later into numerous "sporozoites."

An unbiased consideration of all these more or less incoherent findings and opinions, collected on the foregoing pages, makes it undoubtedly imperative to abandon the a priori negative standpoint at present en vogue in regard to sexualism among the bacteria. It is readily to be admitted that a great deal of what has thus far been recorded upon this problem is rather unsatisfactory. But enough data remain which clearly indicate that more thorough investigations will yield important results.

Besides the normal mode of conjunction, which is practically constantly noticeable in all young cultures, especially from the second to the fourth day, I myself have seen occasionally, when examining the living material in the hanging drop, that two cells of about equal size unite themselves permanently in such a manner as has been described by *Klebs* (1875 a), and I have also occasionally met single large cells of *B. azotobacter* and of other species, which were attacked again and again by small motile bodies, exactly as it has been reported by *Haberkorn* (1882), *Ferrán* (1885), *Dowdeswell* (1889–1890), and by *McDonagh* (1912). Not knowing of any of these publications when these casual observations were made, they have not yet been followed up by special studies, but they may be mentioned here, because they perhaps will help to direct the attention of other investigators to this difficult subject.

More light upon this phase of the life cycles of the bacteria may be expected from careful researches upon the formation and behavior of the bacterial gonidangia, which at the same time will do away with much useless talk about "involution forms." A peculiar ring formation has been described by *Van Tieghem* (1884, p. 110) with *B. amylobacter,* by *Firtsch* (1888) with *V. proteus,* by *Morck* (1891) with *B. radicicola,* by *Schmorl* (1891) with *Streptothrix cuniculi,* by *Burri* (1897) with *B. bernensis,* by *Moro* (1900) with *B. acidophilus,* by *Rosenfeld* (1901) with several members of the *B. septicaemiae* group, by *Stefansky* (1902) with his *B. pyogenes ramosum,* by *P. Ernst* (1902) with *B. fluorescens,* and by numerous authors with various spirochaets. Several of these reports seem to indicate that these rings or loops are much inclined to turn into globules, as was already observed by *Perty* (1852), *Firtsch* (1888), *Morck* (1891), and by *P. Ernst* (1902), and it is not impossible that these globules are able to act later as the "macrogametes" of *McDonagh* and his earlier colleagues before developing to gonidangia.

Whether the conjunction of the young bacterial cells has anything to do with the appearance of the gonidia within these cells, remains to be seen. That, however, the round lateral and terminal regenerative bodies are frequently true zygospores becomes increasingly probable, though it is quite possible that, as with certain fungi, so also with the bacteria, "azygospores" may sometimes take the place of zygospores.

The peculiar triangular forms found with spirilla and other bacteria whose center gradually assumes globular shape while the ends are fading away (see figs. 86 and 87 on Pl. VIII) present another problem which perhaps will find its solution when attacked from this new point of vantage.

How far the formation and germination of endospores is dependent on a previous act of autogamy or heterogamy will have to be decided by further research. Our figure 69 on Plate VI indicates fairly well that the formation of endo- as well as of exospores may be influenced by the conjunction of the parent cells, and the conjunction between the liberated endospores themselves, as visible in figure 284 on Plate XXII, should be accepted at present at least, as an interesting occurrence of unknown physiological value. It should be kept in mind in this connection that analogous facts are known from various fungi, and it seems to be especially suggestive that, for instance, the sporidia of Ustilagineae have been found by *De Bary* (1884, p. 192) to copulate before germinating when kept in a poor substrate (water), but that on a rich substrate they germinate without previous copulation.

It has been pointed out in Chapter III that sometimes endospores, like the bacterial cells themselves, may enter the symplastic stage before reproducing new cells, and it is quite probable that the results obtained by us in this direction have been partially due to our keeping the cultures usually in much less concentrated substrates than are generally used in bacteriological laboratories, substrates, however, which are very favorable to a long-continued development of the bacteria, as was exemplified by the data given on page 189. It is well known that transplantation of well-grown cultures into water exerts a stimulating influence upon the formation of reproductive organs. It also strengthens the tendency of the bacteria to enter the symplastic stage. And the same may hold true in regard to the conjunction of the bacteria, which despite our very incomplete knowledge can be looked upon, like the formation of the symplasm, as a means of placing the continuity of bacterial life upon a broader and safer basis than that afforded by a single cell.

That studies on the behavior of the nuclear material within the bacterial cells during and after conjunction are not very promising at the present time, is hardly to be denied, the difficulties in this case being so much greater than with the yeasts and other lower fungi. However, careful and patient research will undoubtedly secure more evidence that, as has been made probable by the more or less casual observations quoted above, sexual processes also play their rôle in the lives of the bacteria, just as they do in the lives of all other, lower as well as higher, organisms, and that, in this respect also, the bacteria are not those unnaturally rigid things which they were declared to be by the preconceived doctrine of constancy and simplicity, but that they again behave much more like other living beings and, therefore, deserve to be studied like these in all the vagaries which they exhibit in the course of their life cycles.

V. METHODS.

1. ad I: DIFFERENT CELL FORMS.

On pages 37–43 the main points of importance for studies upon pleomorphistic problems have been discussed. In addition, the following references occasionally may prove helpful in further investigations.

In regard to microscopic observations *R. Koch* (1881, p. 6) and *Fraenkel* (1891, p. 86–89) have published most valuable hints for avoiding possible errors due to artefacts, contaminated staining solutions, etc. Equally worth reading is *A. Fischer's* (1899, p. 30) discussion of the vexatious rôle played sometimes by peptones, albuminous, and other substances in dried preparates. For staining, the Congo red adsorption method, as worked out by *Benians,* is highly recommended by *Hort* (1917*a*). According to *Knack* (1915) nigrosin is superior to India ink, and especially suitable for studying living material. Many details concerning dried smears and hanging drop preparations are given in *Hueppe's* book on bacteriological methods (1891, pp. 48–51, 86–99). *Prazmowski* (1912, p. 110) found wax preferable to fat or vaseline for sealing hanging drops, because it does not shut off the air so completely as the last-named substances do. *Schouten* (1905) pointed out that hanging drops of broth often become too acid to allow further growth; placing some 2 per cent KOH below the drop is recommended as preventive measure. *Th. Cohn* (1913) found it useful to change the hanging drop into a thin liquid layer by placing a small cover glass on it, an arrangement which seems, indeed, to be very practical for certain purposes. The hanging agar block method of *Hill* (1902 *b*) gave *Baur* (1905) less satisfactory results than the hanging drop; *Graham-Smith* (1910), who used it extensively, had also to record frequent failures.

The continuous observation of bacterial development under the microscope is often impossible on account of the disinclination of many bacterial cells to grow under such abnormal conditions; moreover, their motility may spoil the result. On pages 38–39 it has been pointed out why the statement, made by some authors. that only those changes should be accepted as correctly ascertained, which have been observed directly and without interruption under the microscope, can not be considered as appropriate. Even *Winogradsky* (1888) had to admit that the movements of the bacterial cells often hindered the continuous observation, which he declared absolutely imperative for solving pleomorphistic problems. And though *DeBary* (1884, p. 137) was undoubtedly right when he said that the continuity of the different phases in the growth of fungi (and bacteria) must be as accurately ascertained as the fact that the apple is a developmental product of the apple tree, certainly neither he nor anybody else would insist that only if this apple has grown from its beginning to full maturity in the laboratory under prescribed conditions and under the never flinching eye of one observer the fact can be accepted as properly proven.

The use of single-cell cultures is another desideratum which is greatly exaggerated by some theorists. Repeated plating coupled with careful microscopic tests furnishes, as has been discussed on page 39, exactly the same results as the single-cell cultures, which generally are less satisfactory on account of lack of growth and greater chances for contamination. Occasionally the fishing methods recommended by *Schouten* (1905–1907), *Barber* (1907–1911), *Nieuwenhuis* (1911), and *Hecker* (1916) will be useful. Usually, however, the India ink method of *Burri* (1909) has much in its favor, especially in connection with the improvements worked out by *Viehoever* (1913, p. 241: dilutions to be made in small test tubes) and by *Troili-Petersson* (1904: droplets to be placed upon gelatin or agar on hollow slide or in Boettcher's chamber). The little-known drop plate method of *Holten* (1893) deserves also further testing.

After having made the dilutions in a good nutrient solution, small droplets are placed upon a glass plate possessing a net work of glass ridges (1 mm. high); another glass plate is put on as cover, and those drops containing only one cell can be marked and the growth studied directly under the microscope. The early method introduced into bacteriology by *Klebs* (1873) to keep the inoculated gelatin in a Geissler chamber, which allows the microscopic study of the isolated germs, offers other obvious advantages for investigations upon the life history of the bacteria. It has already been recommended by *H. M. Ward* (1895), who also made gelatin cultures on cover glasses.

Replacing the Petri dishes by flat square bottles tends further to reduce the possibilities of contamination; and often repeated plating, together with a sufficient number of parallel tests, whose great importance has been pointed out on page 39, makes the experiments as safe as, or even safer than the various modes of single-cell cultures, but generally much more successful.

Frequent transfers from and to the same substrate usually hinder the bacteria to display their natural pleomorphism. Therefore, if not such incomplete results are wanted for some special purpose, long-continued tests on a greater variety of substrates, kept at different temperatures and under otherwise modified conditions, are generally preferable, and they are indispensable if complete and correct data upon the life history of the bacteria are to be secured.

As a rule the substrates recommended for laboratory use are too concentrated, and the large amount of metabolic products accumulating therein often causes the premature death of the cultures, which in less concentrated media continue to exhibit their characteristic alternating mode of life at least for several months. Some recipes for such weak nutrient solutions, suited for soil bacteria, have been given in our first preliminary paper (*Löhnis* and *Smith*, 1916 *a*, pp. 686 and 689), and it was also mentioned there that sterilized soil itself proved to be a very suitable medium, allowing *B. azotobacter* to display all its characteristic cell forms with the greatest precision within a few weeks. "Rejuvenation" in sterilized soil has also been found by *Bredemann* (1909) to be very helpful for reestablishing the common character in many different Amylobacter strains. Cultivation in water has helped *Stamm* (1914) and others to discover important parts of the life cycles of *V. cholerae* and of other organisms, which are much less conspicuous on the standardized substrates. Broth diluted with water furnished *Ferrán* already in 1885 all the different cell forms of the cholera bacillus and gave later *Taddei* (1909) the various types of growth of *Streptoc. pyogenes*, *choreae*, and *erysipelatos*. *Distaso* (1916) recommended diluted serum (1 part serum diluted with 1 part tap water, and digested by trypsin or pancreas).

Increased aeration, which is often desirable when working with solutions can be established either by immersing plates or strips of gypsum partially into the liquid, as has been done with good results, for instance, by *Casagrandi* (1901) and by *Cacace* (1903), or simply by adding a strip of filter paper before sterilizing, so that it stands out about an inch above the solution. Increased atmospheric pressure, together with relatively high temperature, was found by *Arloing* (1908) to be very effective in bringing about the development of clubbed, branched, and of giant forms of *B. tuberculosis*. On the other hand, anaerobiosis allowed *Concetti* (1901) to change the actinomycotic type of growth of *B. diphtheriae* quickly back into the typical, highly virulent rod form, and *Almquist* obtained many of his interesting results with *B. typhosus*, *V. cholerae*, and with other pathogenic organisms by keeping his cultures at temperatures as low as 10–12° C.

The influence of a wider range in acid and alkaline reaction of the substrates deserves to be made the object of detailed studies. Already in 1888 *Wasserzug* noticed that *B. prodigiosus* always produced rods and threads in acid, but coccoid and spiral forms in alkaline broth. *Th. Smith* (1890) saw *B. mallei* grow with a yellow-orange color on acid, but as a gray layer on alkaline substrates. According to *Thiercelin* and *Jouhaud* (1903 *b*) the Enterococcus appears as a typical Streptococcus in slightly acid broth, but alkaline reaction stimulates the development of tetrades. Anaerobic bacilli were more ready to produce their "giant" forms in *Hibler's* (1908) experiments when 1–2 per cent Na_2CO_3 was added to agar, serum, or potato. On the other

hand, *B. typhosus, coli,* and related forms presented their wide pleomorphism to *Hort* (1917 *a*), when kept in distinctly acid broth (usually +10 to +20, sometimes up to +60 phenolphthalein). *Bunker* (1917) noticed that varying hydrogen-ion concentration induced the appearance of all different types of diptheria bacteria desscribed by *Wesbrook.*

For special purposes, especially for securing a quicker development of the various forms, it will sometimes become advisable to increase the amount of certain substances in the substrates, though under such conditions special care must be taken to prevent an early death of the culture. *Albrecht* and *Ghon* (1900), for instance, pointed out that the addition of 5 per cent glycerin or 5 per cent sugar proved to be very useful for studying the pleomorphism of *B. pestis.* And it was with the same organism that *Hankin* and *Leumann* (1897) first found out the stimulating influence exerted by a higher concentration (2½–3 per cent) of common salt. Analogous results with this and numerous other species have been recorded by *Matzuschita* (1900), *Skschivan* (1900) *Rosenfeld* (1901), *Stefansky* (1902), *Maassen* (1904), *Hata* (1908), and others. That most of the cell forms seen by these authors have been wrongly classed as involution forms and that common salt merely speeds up the normal development and induces often, on account of its physiologically drying effect, the production of resting and reproductive organs has been discussed in Chapters I and II.

Other salts, like the lithium compounds tested by *Gamaleia* (1900, p. 207), the rubidium, caesium, magnesium, strontium, baryum chlorides used by *Maassen* (1904), potassium iodide and urea tested by *Péju* and *Rajat* (1906–1907), and by *Wilson* (1907), exert, besides their general osmotic action, more or less specific influences. And this is still more the case with the various antiseptics, such as 0.5 per cent potassium bichromate (*Thiercelin,* 1903), 0.5–1.5 per cent carbolic acid (*Cacace,* 1903), 0.2 per cent saturated alcoholic solution of methyl violet (*Walker* and *Murray,* 1904), or small amounts of $CuSO_4$ (*Garbowski,* 1907*b*).

Special substrates have been used and recommended in many cases, so for developing the branched forms of *B. radicicola* by *Stutzer* (1900–1901), *Hiltner* and *Störmer* (1903), *Buchanan* (1909), *Zipfel* (1911), and many others, for *B. diphtheriae* by *Escherich* (1894, p. 81), *Abbott* and *Gildersleeve* (1903), for *B. tuberculosis* by *Wolbach* and *Ernst* (1903) and by *Wherry* (1913). Egg substrates proved to be of special benefit in investigations upon branching made by *Fraenkel* (1895), *Meyerhof* (1898), *Dorset* (1901 *b*), and *Kodama* (1908), while serum was found to be most useful by *Kohlbrugge* (1901, for water vibrios), by *Vincent* (1902 for branching streptococci) and by *Carpano* (1913 for developing the full pleomorphism of *B. mallei*); continued cultivation of *B. coli* in ascitic fluid enabled *M. E. Abbott* (1900) to fix the coccoid growth, so that it did not revert to the rod form. It goes without saying that the skillful use of many varied substrates, together with such an arrangement of the experiments that the bacteria are allowed to grow under conditions as natural as possible, will lead to the most satisfactory results.

As has been pointed out in Chapter I, the study of symbiotic effects is also of very great importance. Instead of keeping different strains in mixed cultures, as was already done with good result by *DeBary* (1884, p. 503), it may be sometimes preferable to adopt the "double test tube" method of *Smirnow* (1908, the apertures of the smaller inner tube being covered by celloidin), or to add merely the sterilized metabolic products of other cultures, a method which has given remarkably good effects, even when the material was taken from old gelatin cultures of the same species (*B. mycoides,* according to *Nadson* and *Adamović,* 1910).

2. ad II: REPRODUCTIVE ORGANS.

It has been discussed in Chapter II, especially on pages 108–119, that numerous difficulties may arise in the course of investigations upon the formation and the further behavior of the various types of reproductive organs of the bacteria, and that generally their characteristic function, viz., the reproduction of new vegetative cells, will have to be studied directly, to eliminate all doubtful points, which can not be definitely settled otherwise. It must be borne in mind, however, that the conditions usually prevailing in the hanging drop or agar block preparations are often not favorable to the development of new cells, and that, therefore, a few negative results obtained in this manner can not be accepted as a safe basis, on which to found final

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conclusions as to the reproductive or nonreproductive character of some problematical body. It needs hardly to be emphasized that especially the study of the small gonidia, as well as that of the more conspicuous regenerative bodies, necessitates great care in making microscopic examinations. When discussing *A. Fischer's* much exaggerated plasmoptysis hypothesis, it has been pointed out that a very thorough cleaning of the slides and cover glasses (by potassium bichromate + sulphuric acid) is absolutely necessary. Great care in making and fixing smears is equally essential, as many of these frail things will not stand the ordinary rubbing and heating; the round regenerative bodies are especially liable to be materially altered by excessive heat. Lack of care in rinsing the stained preparate may wash away many of the slightly fixed bodies.

More than ordinary cleanliness is also essential for cultural experiments. Sterilization of vessels and substrates kills the regenerative bodies more easily than the endospores, but they still may become visible in the microscopic field and cause considerable error. As figure 295 on Plate XXIII a photograph has been reproduced (*Löhnis* and *Smith*, 1916 *b*, original fig. 57), showing various vegetative cells and regenerative bodies of *B. Azotobacter* developing from the symplastic stage, and in figure 296 (reproduced from original fig. 58, l.c.) the same material is demonstrated after it had been heated for 30 minutes in the autoclav at 20 pounds pressure. It is evident that substances and vessels, containing such bodies, are very liable to lead to erroneous results. Careful comparative studies of steril controls will always be advisable, and occasionally the treatment of the glassware with chromic acid and the filtration of the substrates through Berkefeld, Chamberland or asbestos filter (*Heim*, 1906, p. 35) will become necessary.

Transplanting vigorously growing cultures of several days age into water, mineral solutions, on substrates containing a relatively high amount of salt, or keeping them at comparatively low temperatures, are the means which have been used most successfully to stimulate the development of reproductive organs. Transfers made into water gave *Van Tieghem* (1879 *b*) very satisfactory results in his studies upon the spore formation of the bacteria, including the arthrospores of spirochaets. In the same way *Braem* (1889) got many different types of reproductive organs (regenerative bodies, gonidangia, etc.), which he mistook for signs of "degeneration," and *Rullmann* (1900) recorded analogous findings in mineral solutions as being "Hungerformen". Many of the "abnormal" cell forms appearing on salt substrates leave no doubt about their being regenerative bodies or gonidangia, though they, too, were usually classed as "involution forms." Especially the investigations made in this direction by *Matzuschita* (1900) and by *Maassen* (1904) have furnished numerous data, which may be used as a basis for further, more thorough research. *Almquist* (1904), *Fuhrmann* (1906), and *Hammerl* (1906) ascertained that these various forms, whose development is favored by increased salt content of the substrate, are indeed reproductive organs. The first-named author (*Almquist*, 1904–1916) has also contributed much material illustrating the stimulating effect of low temperatures (10–15° C.) upon the production of regenerative bodies, especially by pathogenic organisms. Results secured by *Schürmayer* (1900) and by *Arloing* (1908) in regard to the formation and multiplication of gonidia, regenerative bodies, and of gonidangia of the tuberculosis group are in good agreement with *Almquist's* observations.

Change in reaction naturally will also exert its influence. *Garbowski* (1907*b*), for instance, noticed in the course of his studies upon variability and spore formation of *B. luteus sporogenes* that on nitrate agar endospores were readily produced, while on sugar or glycerin-ammontartrate agar only darkly staining inflations became visible (either regenerative bodies or gonidangia), and that this difference was due to an alkaline reaction developing in the nitrate agar and an acid one in the glycerin or sugar agar. *Bredemann* (1909) has collected more evidence in regard to the favorable influence of an alkaline reaction upon spore formation. On the other hand, it seems equally advisable to study more closely the specific effect of a more or less acid reaction upon the production of the other types of reproductive organs.

Simonds (1915) has pointed out that besides composition and reaction of the media the influence of symbiosis should not be overlooked. Experiments with the double test-tube

method (see p. 207), or the use of substrates containing the metabolic products of the same or of another species, seem to be very recommendable also in this case.

Increased or decreased aeration may be equally helpful. *Archangelski* (1883), e. g., found that the small round reproductive organs (gonidia and regenerative bodies) of *B. anthracis* multiplied readily as such in absence of air, but reproduced promptly rods in presence of air. *Bredemann* (1909), on the other hand, had a constant aerobic culture of what he calls "microoidia" of the anaerobic *B. amylobacter*.

That the gonidia show much variation in their staining reaction has been emphasized in Chapter II. Often the common staining, especially with fuchsin, is applicable; sometimes, however, these bodies are very little inclined to take any stain at all. *Lugol's* solution has been found helpful in such cases by *Kuntze* (1904) and by *Růžička* (1908); but many authors give preference to one or the other kind of vital staining. Some valuable hints upon the principles of this method may be found in papers written upon this subject by *Pfeffer* (1886), *Campbell* (1888), *A. Fischel* (1903), and *Ph. Eisenberg* (1913, pp. 437–446). Methylene blue has been used as early as in 1885 by *Babes* in his studies upon the motile "granules," which he discovered in the cells of *V. cholerae*, and it has been equally preferred by *Zettnow* (1897), *Nakanishi* (1900 *a*, 1901), *P. Ernst* (1902), *Mencl* (1910), *Meirowsky* (1914 *b*), and others. *Amato* (1908) recommended "Brillantkresylblau," *Balfour* (1912), especially for blood preparates, toluidin blue, and *Prazmowski* (1912 p. 148) got most satisfactory results with a mixture of methylene green and fuchsin. Identical results were obtained by *Swellengrebel* (1906) when the vital staining was replaced by the Heidenhain method, applied to the dried preparate, fixed with 35 per cent formalin. And besides this, the various modifications of the Romanowsky-Giemsa method have been repeatedly found to be of special value for such studies, as may be seen from the publications of *Zettnow* (1899), *Feinberg* (1900), *Giemsa* (1904–1914), *Herzog* (1910), and of *Betegh* (1911), while *A. Meyer* (1912, p. 61) takes the opposite standpoint. That the cytological theories and the microchemical methods of the last-named author (l. c., pp. 209–247) have not met with general approval was mentioned in Chapter II (p. 113).

A special staining method for gonidia has been recommended by *Fedorowitsch* (1902). It is a modified Gram method and deserves further testing, as frequently the gonidia have shown positive reaction with this method, even if the parent cells themselves are Gram-negative. Occasionally one or the other of the various methods may become applicable which have been developed for staining the "granules" in diphtheria, tubercle, and leprosy organisms by *Lutz* (1886, p. 87), *Unna* (1887, pp. 12, 15), *A. Neisser* (1888, p. 175), *Spengler* (1907), *Betegh* (1908–1909), *Knoll* (1910), and *Fontes* (1910).

The dark field method, which *Meirowsky* (1914 *b*, p. 15) and others found to be very useful for such investigations, is not restricted to living preparates. Dried smears also often give very good pictures, as was pointed out recently by *Leishman* (1918), and as we have shown in the photograph reproduced as figure 234 on Plate XVIII (from *Löhnis* and *Smith*, 1916 *a*, original fig. 42).

Because the gonidia often, though not always, display a slightly but distinctly higher resistance than their parent cells against various deleterious influences, it is to be expected that more detailed investigations will also provide us with means to separate the gonidia from the vegetative cells. Observations made by *Fuhrmann* (1908) and others indicate, for instance, that a comparatively high concentration of NaCl is much less detrimental to the gonidia than to the cells, and the same seems to hold true in regard to a weak KOH solution, according to some findings by *Frank* (1890) and by *Jessen* and *Rabinowitsch* (1910).

As the ordinary laboratory substrates very seldom allow the direct upgrowth of isolated gonidia, the positive results obtained in many experiments upon so-called heterogenesis, where, in fact, dying or dead plasma of fungi and algae, not altered by heating, proved to be a very suitable medium for securing new upgrowth of bacteria from their gonidia, seem to promise equally good results for new methods to be developed along these lines. In addition to what has been said upon this subject on pages 148–150, it may be pointed out that especially

the algae experiments made by *Dunbar* (1907) and the blood tests of *Fokker* (1887, p. 72) deserve to be carefully studied anew. Autolyzed tissue (liver, kidney, brain, etc.) may be useful, too, in some cases; *Couret* and *Walker* (1913) obtained good growth of pure cultures of parasitic amobae on it.

When experimenting with the filterable part of the gonidia, still further difficulties are to be overcome. Faulty bougies or too long continued filtering under too high pressure are especially liable to cause incorrect results. *Doerr* (1911) and *Fontanel* (1913) have published valuable papers upon the technique, thus far developed, and its proper use. But especially in regard to securing a new development of normal bacterial cells from the filtered gonidia practically all remains to be done. However, results obtained by *Nocard* and *Roux* (1898), *Nocard* and *Leclainche* (1903–1905, Vol. I, p. 449), *Bordet* (1910), *Borrel* et al. (1910), *Almquist* (1911–1917), *Hort* (1917 *a*), and in our own experiments (*Löhnis* and *Smith*, 1916 *a*, p. 695), though still very incomplete, call for a more thorough study of these problems. That occasionally colloid granules may become a source of error was discussed by *Huntemüller* (1916) and by *Hallenberger* (1917).

Observations upon the formation and germination of the lateral and terminal round regenerative bodies and of arthrospores generally present no more difficulties than do analogous experiments with endospores. As soon as their increased resistance is more completely known, their separation from the vegetative cells by moderate heating or by thorough drying will become an easy task. Some data recorded by *Berestneff* (1907), *Rodella* (1908), and by *Almquist* (1916) are already quite satisfactory. Cultivation on serum favored sometimes distinctly the pure growth of round regenerative bodies (*E. Klein*, 1900; *E. de Negri*, 1916).

Because in stock cultures the endospore formation often shows a tendency to vanish more or less completely, repeated pasteurization may be used to prevent this change, as was recommended by *Beijerinck* (1901 *a*). To suppress the spore formation experimentally numerous methods are available. Often the use of small amounts of antiseptics, first tried successfully by *Roux* (1890), will give the best results; in other cases cultivation in milk (*Grassberger*, 1902), adding of eosin to the substrates (*Noguchi*, 1908), keeping the cultures at nearly maximal temperatures (*Ph. Eisenberg*, 1914) or other means may be preferable.

For the regeneration of endospore formation *C. Phisalix* (1892) found the cultivation in blood most successful with *B. anthracis*, while *Grassberger* (1905) and *Grassberger* and *Schattenfroh* (1907) saw best results with their anaerobic butyric acid bacilli when sugar was added to the substrates. As the regeneration of a lost spore formation is fundamentally not very different from the new development of this faculty in a strain (or so-called species) which thus far has appeared as being entirely and constantly asporogenous, the same method which promises the best results in the latter case, viz. a careful study and repeated heating of the intermediate stages between regenerative bodies or gonidangia and endospores developing from the symplasm will also undoubtedly in many cases secure quicker and always less haphazard results than the methods first mentioned.

3. ad III: SYMPLASM.

For obtaining well developed bacterial "plasmodia" *W. Winkler* (1899) found it most useful to place pieces of raw meat or potato into sour beer-wort, slightly acid bouillon, or a decoction of mushrooms. After 24–36 hours the "plasmodia" were seen to grow forth and soon after they began to form bacterial cells, which later separated themselves. On page 169 it has been mentioned that *Klebs* (1883 *b*) has directly observed under the microscope how the symplastic masses of the tubercle bacilli sprouted out from cuts of tubercular tissue kept in a well aerated chamber. In most cases it is by no means difficult to find out by daily testing of cultures one to several weeks old when the formation of the symplasm reaches its maximum and the regeneration of new cells begins to take place, provided that the points mentioned on page 206, concerning suitable cultural conditions have not been overlooked.

Transfer of small amounts of the symplasm in the common manner, or after picking out single flakes or clumps with one or the other of the various single-cell methods (discussed on

page 205, will occasionally give more conclusive results than the continued study of the material, kept in the old substrate.

Observations made with the unstained living material in the hanging drop have usually not given satisfactory results in the cases where I have employed this method. The irregular surface and density of these clumps and flakes causes nearly always such abnormalities in refraction and reflection of the light that the new formation of bacterial cells could not be accurately followed in this way. Movements within the slimy masses increase these difficulties. On the other hand the possibility can not be denied that occasionally good results will be secured. *Růžička* (1903), for instance, seems to have been more successful with this method.

Small flakes of symplasm, especially those formed by filterable gonidia, give very good pictures in the dark field; but, as was pointed out by *Leishman* (1918), the strong light seems to check all further development. Possibly some mode of vital staining will help to overcome the difficulties standing in the way of studying the living material.

However, the photographs reproduced on Plates XVIII to XXI will prove sufficiently, I believe, that stained preparations can furnish many interesting data, especially when they are made from the same culture in frequent intervals. That the staining qualities of the symplasms vary widely has been discussed on pages 182–183, and on page 178 it was pointed out that and why photomicrographs of such preparations are always rather inferior to the original. According to *Weigert* (1875) hematoxylin has proved to be most useful for staining bacterial "zoogloeas" within the tissue, but *Klebs* (1878) saw it act only upon the "granules" (the regenerative units) within the slime. *Herzog* (1913) found besides methylene blue, giving the metachromatic reaction, Giemsa solution best suited, which stains the regenerative units red, like the "eosinophilic" granules in leucocytes. It is not impossible that one or the other of the color reactions used for amyloid and hyalin substances, described by *Lubarsch* (1903), may also find application in investigations upon bacterial symplasm.

The comparatively high resistance of the symplasm against acids and alkali, which *W. Winkler* (1899) has made use of for separating bacterial "plasmodia" from surrounding bacterial cells, also allows, if necessary, a thorough cleaning of the fixed smear, especially the solving of precipitates, which otherwise might disturb the picture. Great care in rinsing, however, is essential, because, as *Fokker* (1882) has already noticed, the fixation of the symplasm by heat, as well as by alcohol, is sometimes very incomplete.

Certain substrates, especially those made up from meat, peptone, etc., may often present vexatious flakes and clumps, which react like genuine symplasm, but which are either coagula from the ingredients used, or, though real symplasm, do not belong to the cultures under experiment, but were produced by bacteria which have grown on the ingredients before they were used for making the substrates. As with the regenerative bodies to be found in many substrates, here also careful comparative tests of the steril media are indispensable. Figure 297 on Plate XXIII shows such a doubtful flake from sterile beef agar (*Löhnis* and *Smith,* 1916 *b*, original fig. 61). It looks exactly like some real symplasm, for instance, like that of *B. fluorescens,* whose transformation into pale oval cells was illustrated in figure 263 on Plate XXI. Figure 251 on Plate XX (symplasm of rods and spores of *B. azotobacter*) may serve as another object for comparison. Naturally, a final decision can be reached with such dead or "fake" symplasm only by carefully ascertaining whether or not it is able to produce new cells.

It is easily understood that transfers made at the same time from one culture, containing large amounts of symplasm, into various substrates which are to be kept under different conditions, will offer excellent opportunities for securing an accurate insight into the characteristic behavior of a species. Careful, repeated heating of the symplasm and of the regenerative bodies developing from it, has proved to be the most promising way for inducing experimentally sporulation in a strain, which had never formed endospores before. That a very good starting point for experiments on the effects due to symbiosis will be furnished by cultures containing the bacteria in their symplastic stage has been mentioned above (p. 188);

and it was pointed out, too, that long-continued observations upon the same culture (in parallel sets) will contribute much valuable material toward the solution of problems concerning the so-called involution forms, bacterial variation, mutation, etc.

4. ad IV: CONJUNCTION.

Hardly any special data are available at the present time as to the best manner of studying bacterial conjunction. Experiments with the living material at the right time (usually from the second to the fourth day) are most recommendable. Because the motility of the cells is often a rather disturbing factor, their incarceration into the meshwork of fine cuts of elder pith, as recommended by *Fuhrmann* (1908), may be tried. Contact preparates give often, as was shown by several of the photographs, much better pictures than do smears, wherein the fine connections are easily destroyed. If by such tests the right moment has been fixed, the study of the living material should be started. Occasionally vital staining may be helpful.

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SUBJECT INDEX.

[Page numbers marked by * refer to illustrated discussions. Abbreviations following species names refer to chapters on morphology (M), reproduction (R), symplasm (S), conjunction (C).]

Plates A to S and I to XXIII.

[N. B.—The page numbers in () refer to the pages where the illustrations have been discussed.]

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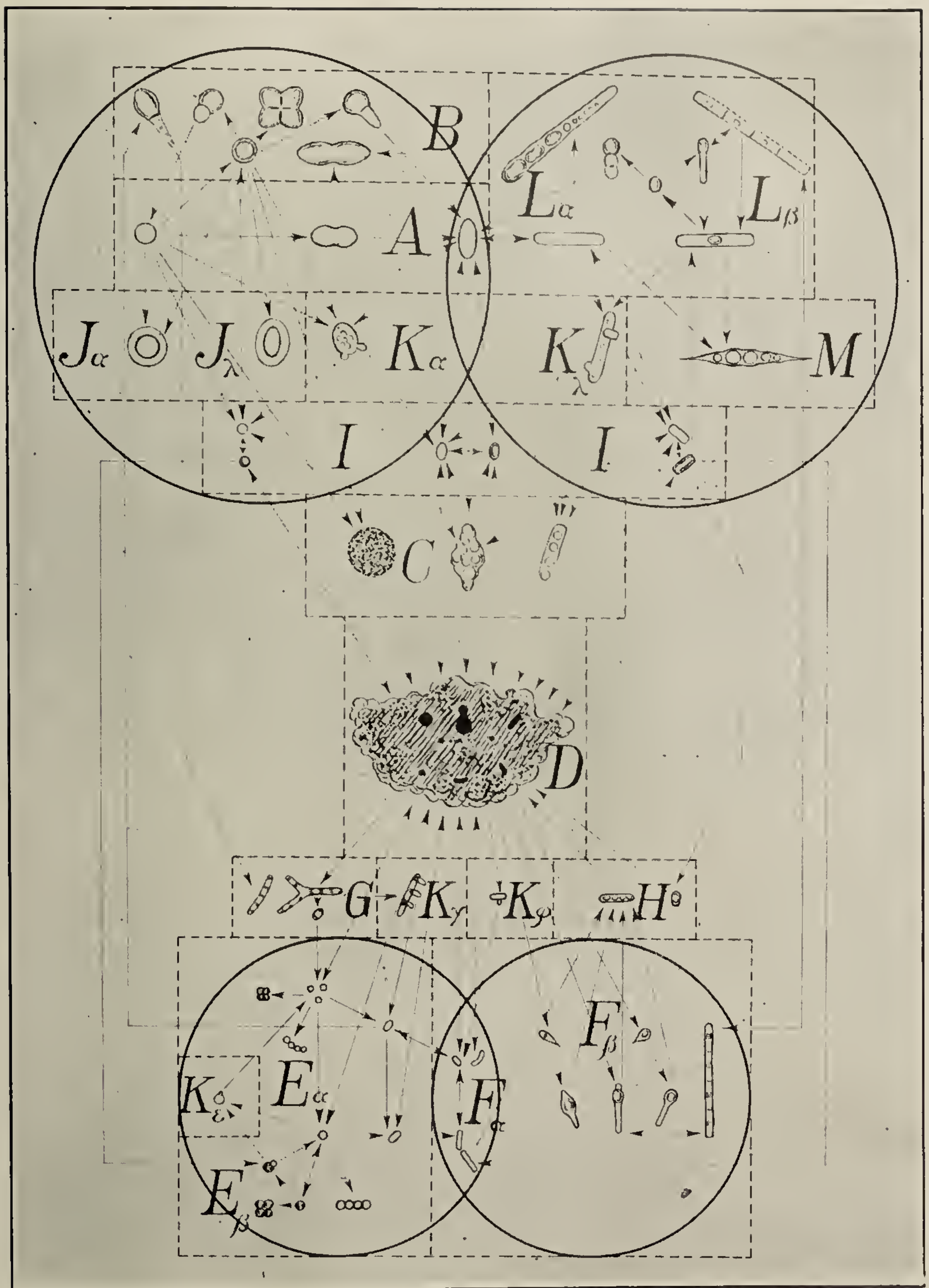
PLATE A.

FIG. 1 (p. 36).—Life cycle of *B. azotobacter.* The broken straight lines divide the different types of growth indicated by the letters A to M. The Greek letters α to λ refer to subdivisions. The single and double pointed arrows indicate the development of one form from another. The four circles confine, in every case, all those forms which represent together a rather constant mode of life, and which have been usually considered as bases for establishing separate species. *Löhnis* and *Smith* (1916 *a*, p. 678).

FIG. 2 (p. 45).—Morphological changes of *Micrococcus gonorrhoeae.* *Herzog* (1913, original fig. 6).


B
A
L_α
L_β
J_α
J_λ
K_α
K_λ
M
I
I
C
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G
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F_β
K_ε
E_α
F_α
E_β

Fig. 1.

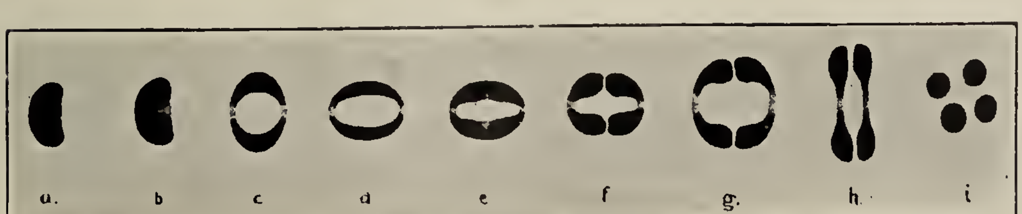

a b c d e f g h i

Fig. 2.

PLATE B.

FIG. 3 (p. 46).—Pleomorphism of streptococci. *Babes* (1895, original fig. 2). ×800.

4 (p. 47).—*Leuconostoc hominis Hlava* (1902, original figs. 3–6). ×1,000.

5 (p. 50).—Proteusartiger Luftbacillus. *Matzuschita* (1902, original figs. II–V). ×1,000.

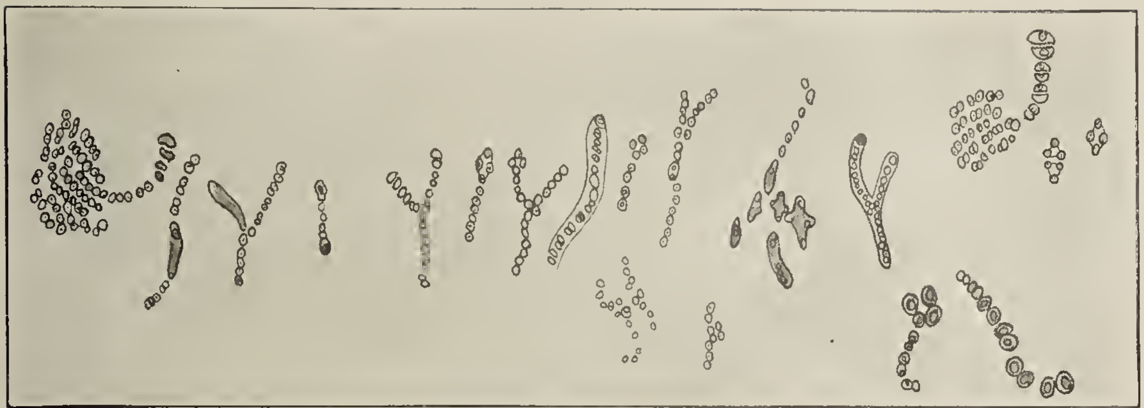


Fig. 3.

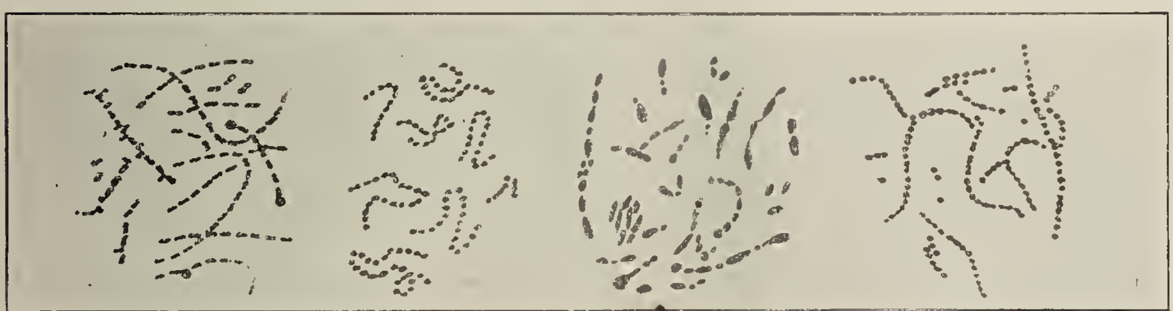


Fig. 4.

Fig. 5.

PLATE C.

FIG. 6 (p. 49).—*Urosarcina Hansenii Miquel* et *Cambier* (1902, original fig. 172) ×1,000.

7 (p. 50).—*Bacterium merismopedioides Zopf* (1883, original fig. 19). ×900.

8 (p. 50).—*B. bifidus communis Tissier* (1900, original figs. 4 and 6). Branching and "formes vésiculeuses". ×1,000.

9 (p. 52).—*B. funduliformis Hallé* (1898, original fig. 3). ×1,000.

10 (p. 52).—Anaerobic bacilli from meningitis. *Ghon, Mucha* and *Müller* (1906, original figs. 6, 20, and 9). ×1,000.

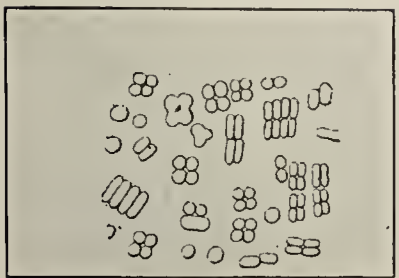


Fig. 6.

Fig. 10.

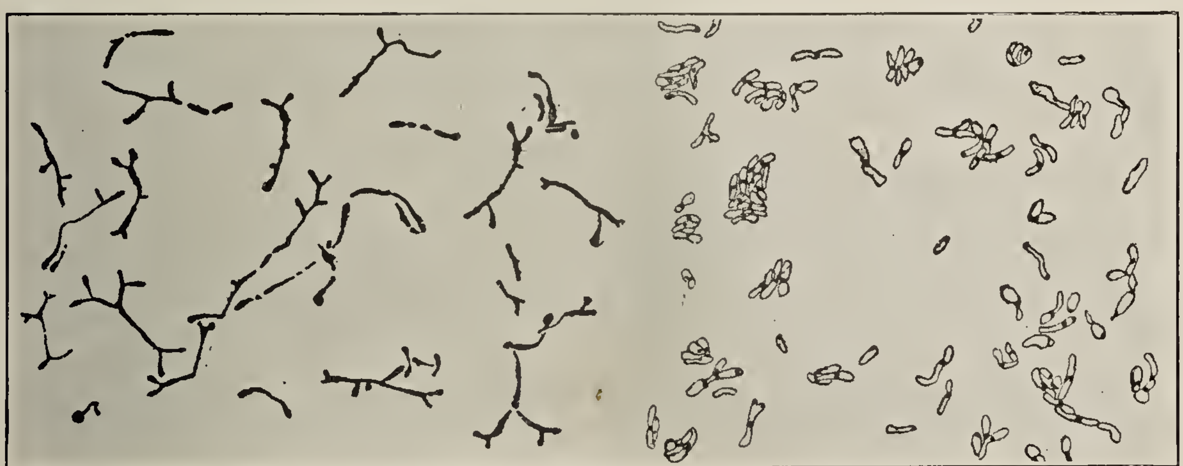


Fig. 8.

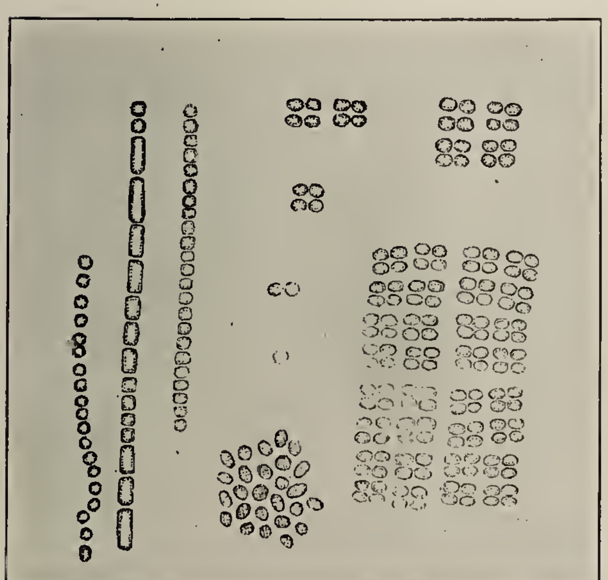


Fig. 7.

Fig. 9.

PLATE D.

FIG. 11 (p. 53).—*B. pestis.* *Albrecht* and *Ghon* (1900, original figs. II, 2–4; III, 5 and 9). ×1,000.

12 (p. 54).—*B. influenzae.* *Crookshank* (1896, original fig. 122, p. 249). ×1,200.

13 (p. 55).—*B. involutus* *Waelsch* (1905, original figs. 4 and 6). ×1,000.

14 (p. 55).—*Proteus hominis capsulatus* *Bordoni-Uffreduzzi* (1888 *b*, original fig. VII, 3). ×750.

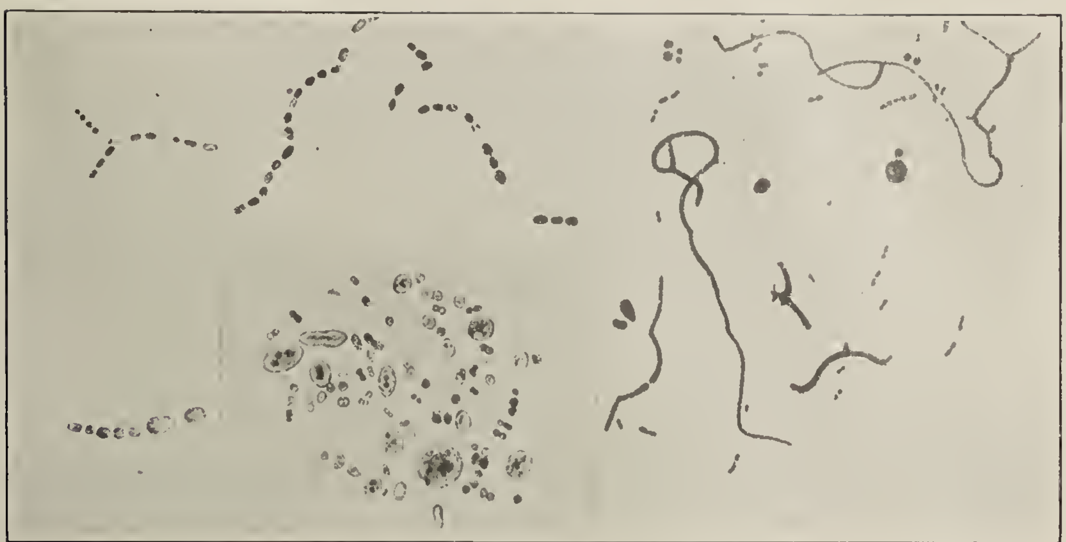


Fig. 11.

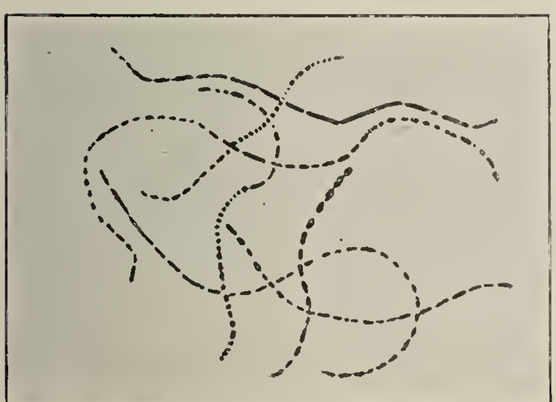
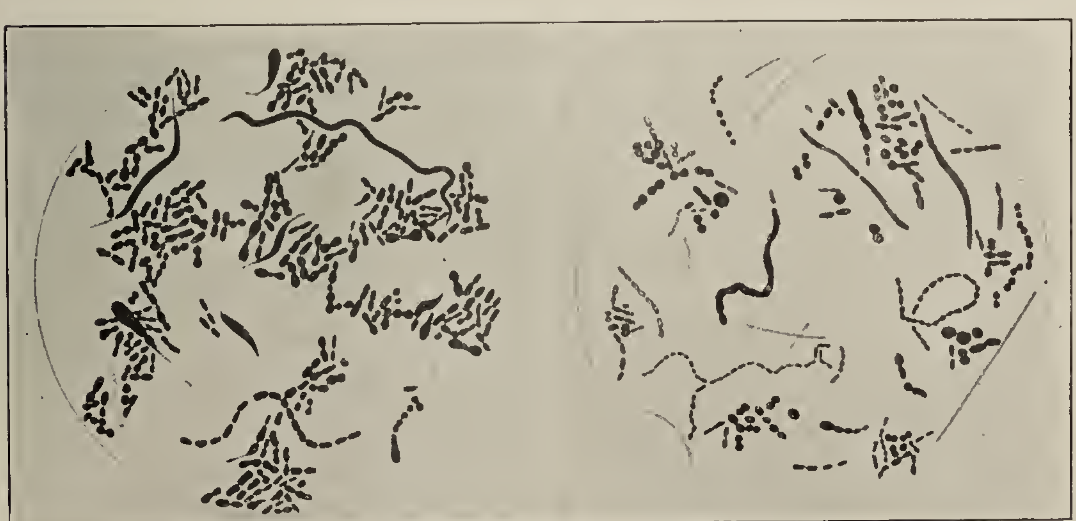


Fig. 12.

Fig. 14.



a *b*

Fig. 13.

PLATE E.

FIG. 15 (p. 58).—*Bact. aceti E. Chr. Hansen* (1879, original fig. 77, 1911). ×1,000.

16 (p. 59).—*B. radicicola*. *Conn* (1900, original fig. 26, p. 99). ×1,000.

17 (p. 62).—*Metallacter Bacillus Perty* (1852, original fig. XV, 26 *a*). ×1,000.

18 (p. 62).—Different cell forms of bacilli. *Nägeli* (1877, original fig. 2).

19 (p. 62).—"Glycerin-Aethylbacterie" (Fitz). *Buchner* (1882, original fig. 10). × 4,000.

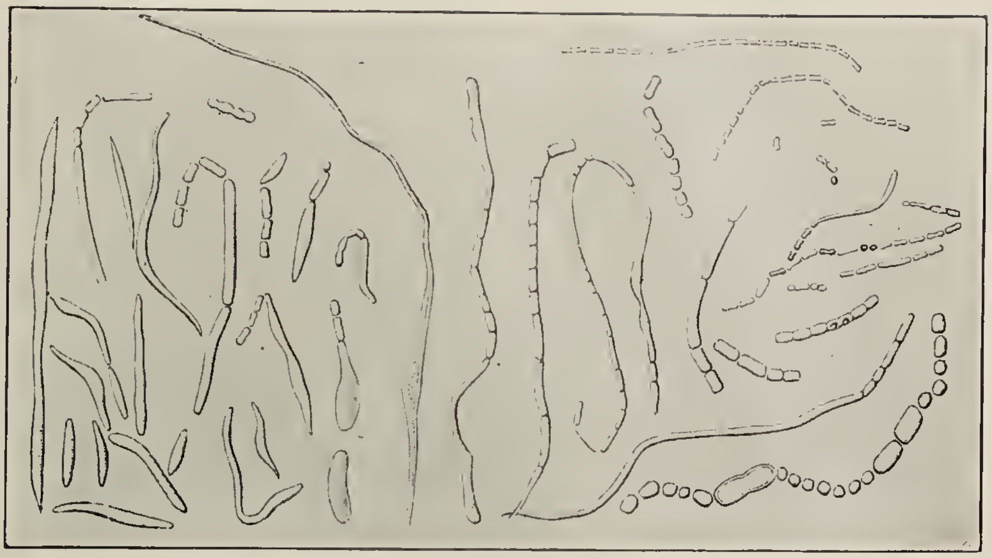


Fig. 15.

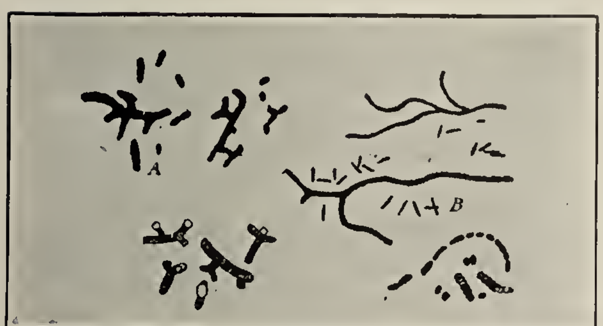


Fig. 16.

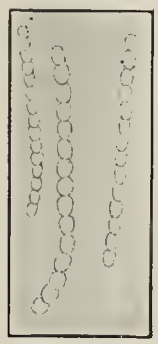


Fig. 17.

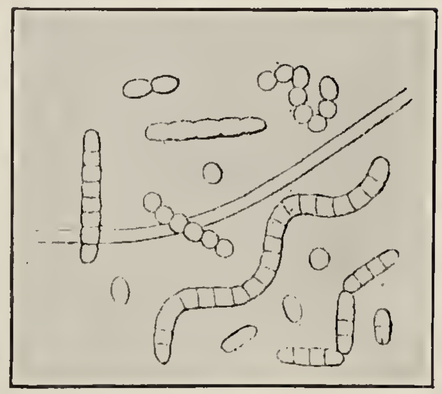


Fig. 18.

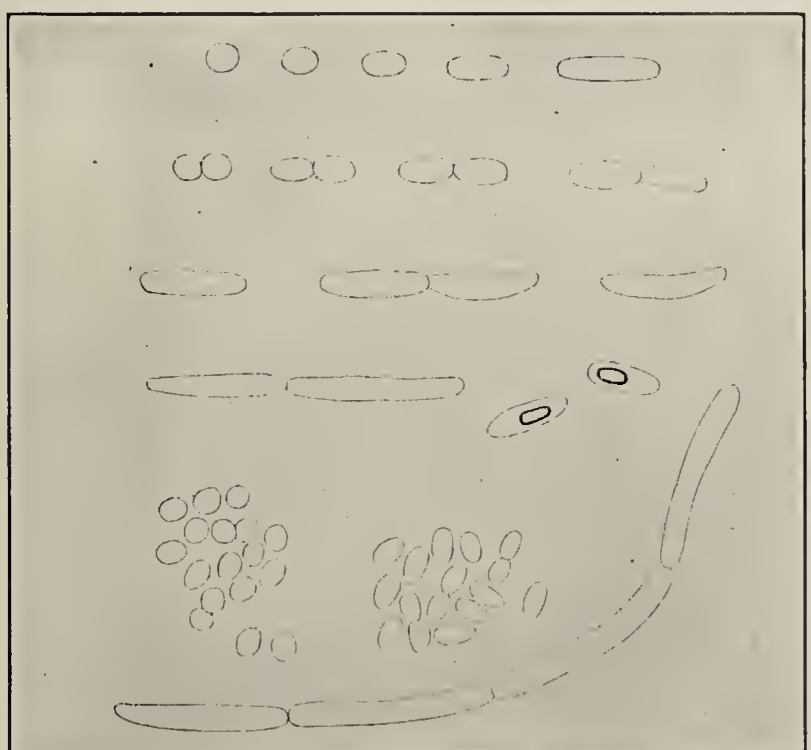


Fig. 19.

PLATE F.

FIG. 20 (p. 62).—*Bac. mycoides.* *Olsen* (1897, original fig. V, 14). ×900.

21 (p. 63).—*B. anthracis.* *E. Klein* (1883, original figs. XXI, 1–3) ×1,000.

22 (p. 63).—*B. anthracis.* *E. Klein* (1885, original fig. 77, p. 109). ×450.

23 (p. 63).—*B. anthracis.* *E. Klein* (1894, original figs. I, 1 and 2). ×1,000.

Fig. 20.

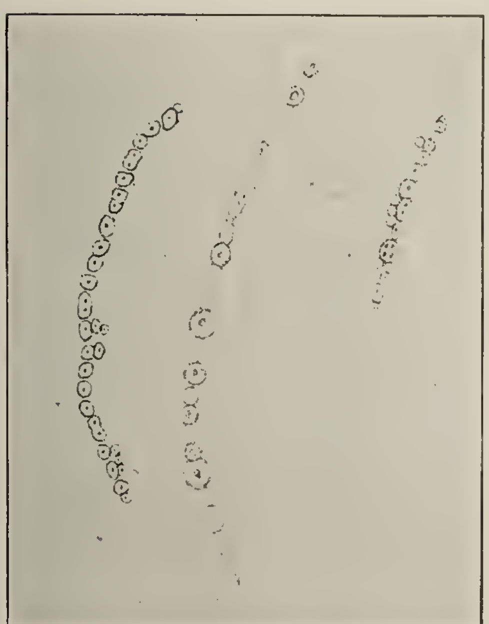


Fig. 21.

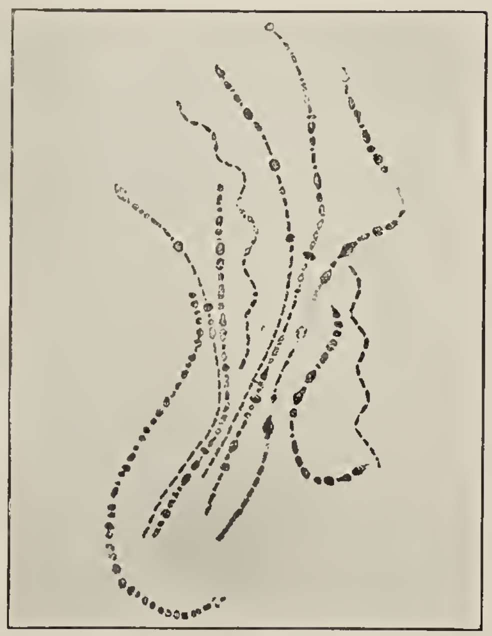


Fig. 22.

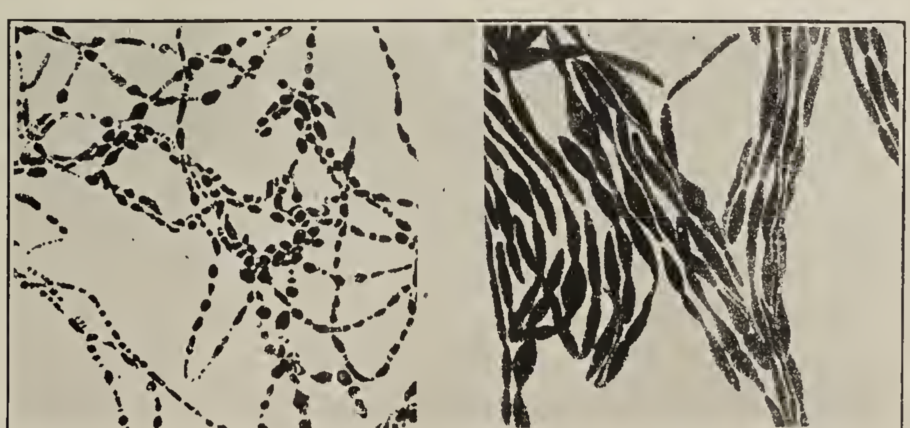


Fig. 23.

PLATE G.

Fig. 24 (p. 65).—*B. tumescens Zopf* (1883, original fig. 23, p. 66). ×900.

25 (p. 66).—*Clostridium butyricum* (above) and *Clostridium Polymyxa* (below), *Prażmowski* (1880, original figs. II, 1, 2, 6, 7). ×1,020.

26 (p. 66).—"Micro-oidia" of *B. amylobacter*. *Bredemann* (1909, original figs. II, 32–36). ×2,450.

Fig. 24.

Fig. 26.

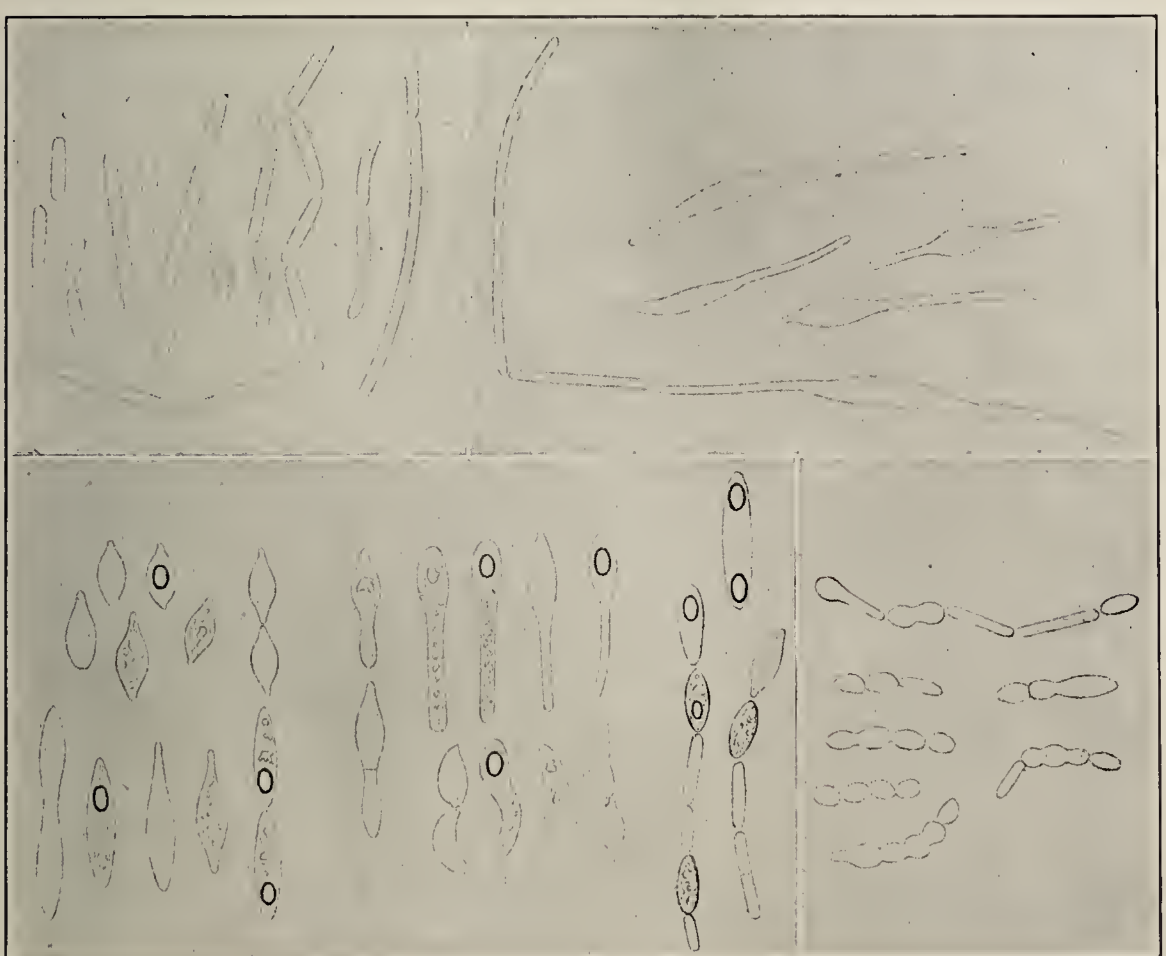


Fig. 25.

PLATE H.

FIG. 27 (p. 67).—*B. Chauvoei, Ghon* and *Sachs* (1903, original figs. 13, 14, 16–18). ×1,000.

28 (p. 68).—*Vibrio Rugula Prazmowski* (1880, original figs. I, 10, and 11). ×1,020.

29 (p. 72).—*Spirillum endoparagogicum Sorokin* (1887). ×1,375.

30 (p. 73).—*Spirillum rubrum. Meirowsky* (1914 *b*, original figs. V*b*, 6 and 7). ×2,000.

31 (p. 73).—*Spirochaeta icterohaemorrhagica Inada* et al. (1916, original figs. 69 and 70).

32 (p. 75).—*Bact. repens Miehe* (1913, original figs. 11, 9, and 10). ×1,120–1,200.

33 (p. 77).—*B. mallei. Marx* (1899, original figs. 1–4).

Fig. 27.

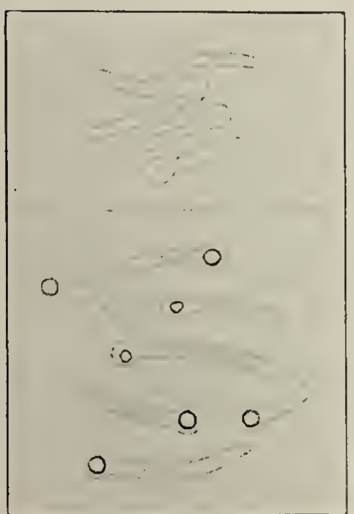


Fig. 28.

Fig. 29.

Fig. 30.

Fig. 31.

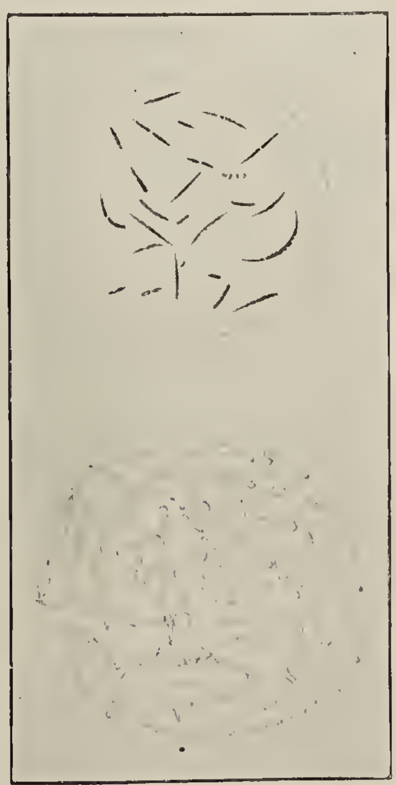


Fig. 32.

Fig. 33.

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PLATE J.

FIG. 34 (p. 80).—*Pseudo-diphtheria bacilli*. *Babes* (1895, original fig. 3). ×800.

35 (p. 81).—*B. enzymicus* *Mellon* (1917, original fig. 2, p. 88).

36 (p. 82).—*B. leprae*. *Lutz* (1886, original figs. 7–11, p. 81). ×1,000.

37 (p. 82).—*B. leprae*. *Kedrowski* (1910, original fig. 37). ×1,000.

38 (p. 84).—*B. tuberculosis*. *Metchnikoff* (1888 *a*, original fig. V, 20). ×1,200.

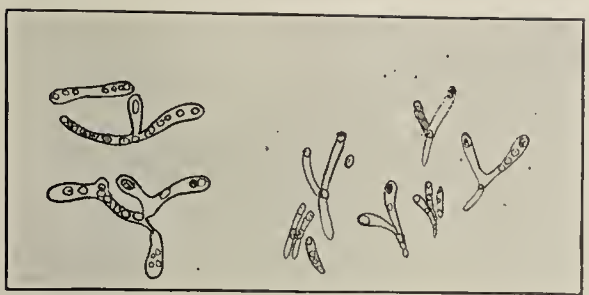

Fig. 34.

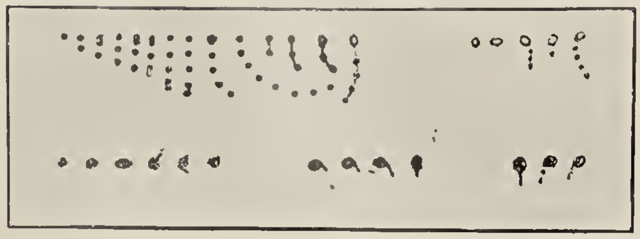

Fig. 36.

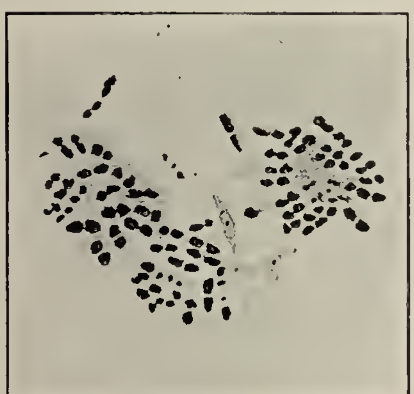

Fig. 35.

Fig. 37.

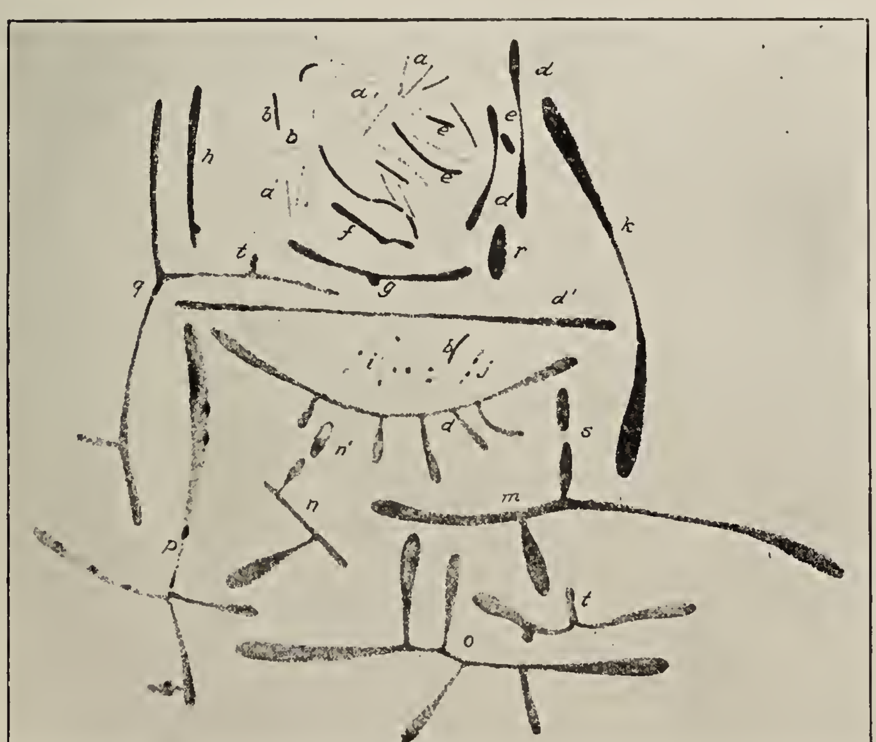

Fig. 38.

PLATE K.

FIG. 39 (p. 87).—Cladothrix (*a–f*) and Actinomyces (*g–i*). *Migula* (1900, original fig. 45, p. 39). *e* and *h* ×500; all others ×1,000.

40 (p. 91).—*Sporonema gracile Perty* (1852, original fig. 26 on Pl. XV). ×1,000.

41 (p. 92).—Germinating gonidia. *Rindfleisch* (original fig. XVIII, 1).

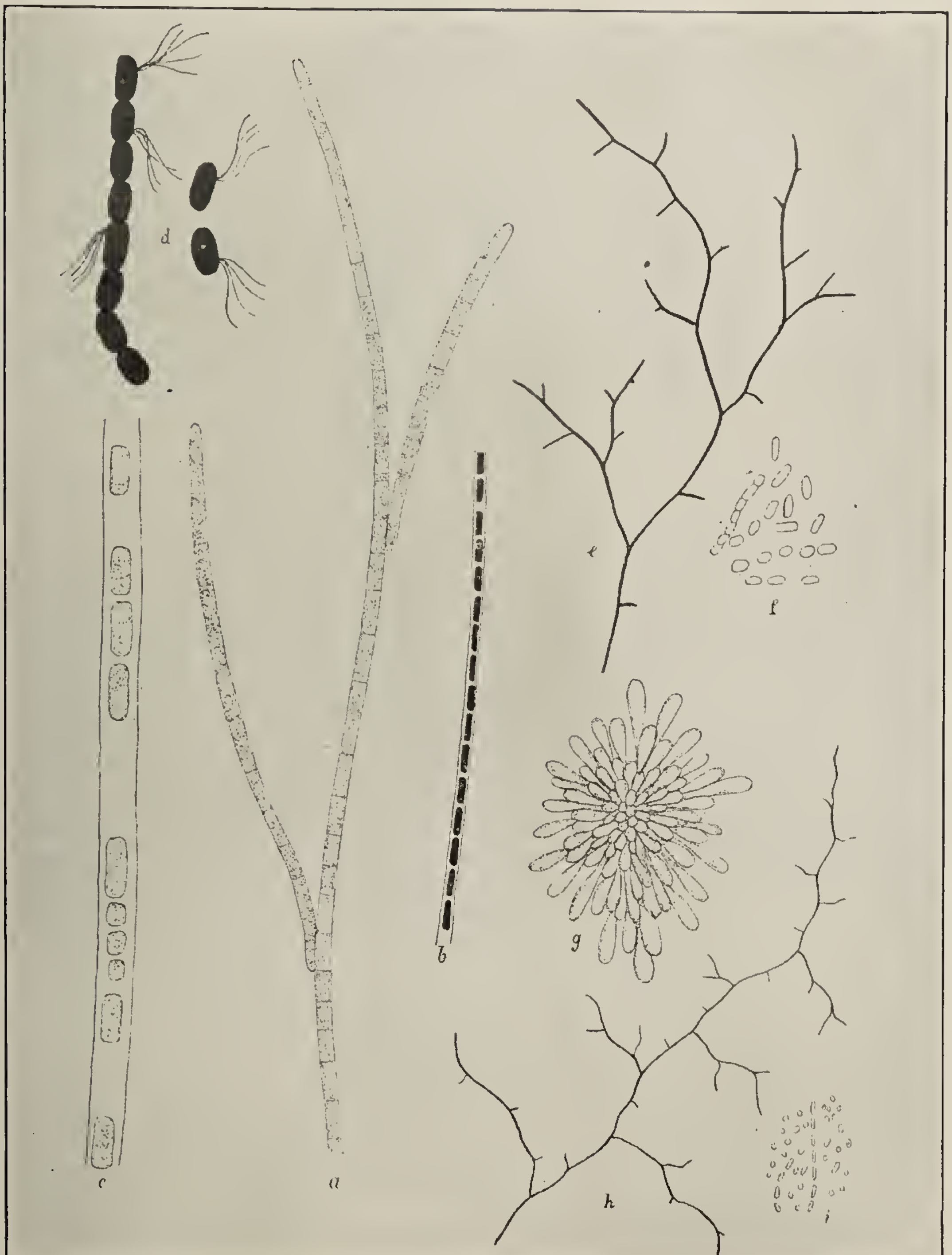

Fig. 39.

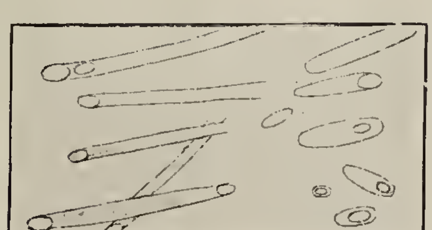

Fig. 40.

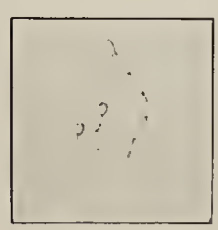

Fig. 41.

PLATE L.

FIG. 42 (p. 91).—Gonidia and Spirilla. *Perty* (1852, original figs. 28, 29B, and 31 on Pl. XV). ×1,000.

43 (p. 92).—"Sporangium" and "spore" of Crenothrix. *F. Cohn* (1870, original figs. 11 and 13). ×500–800.

44 (p. 93).—Formation of gonidia and gonidangia. *Billroth* (1874, original fig. 36). ×1,185.

45 (p. 93).—Formation and liberation of gonidia. *Billroth* (1874, original fig. 42). ×1,185.

46 (p. 94).—*Phragmidiothrix multiseptata*. *Engler* (1882, original fig. 24). ×400.

Fig. 42.

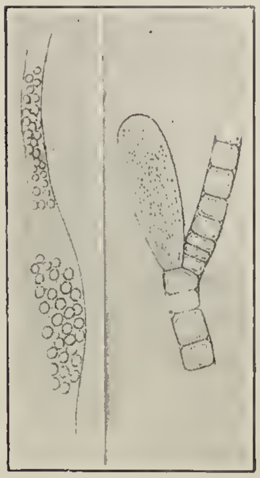

Fig. 43.

Fig. 44.

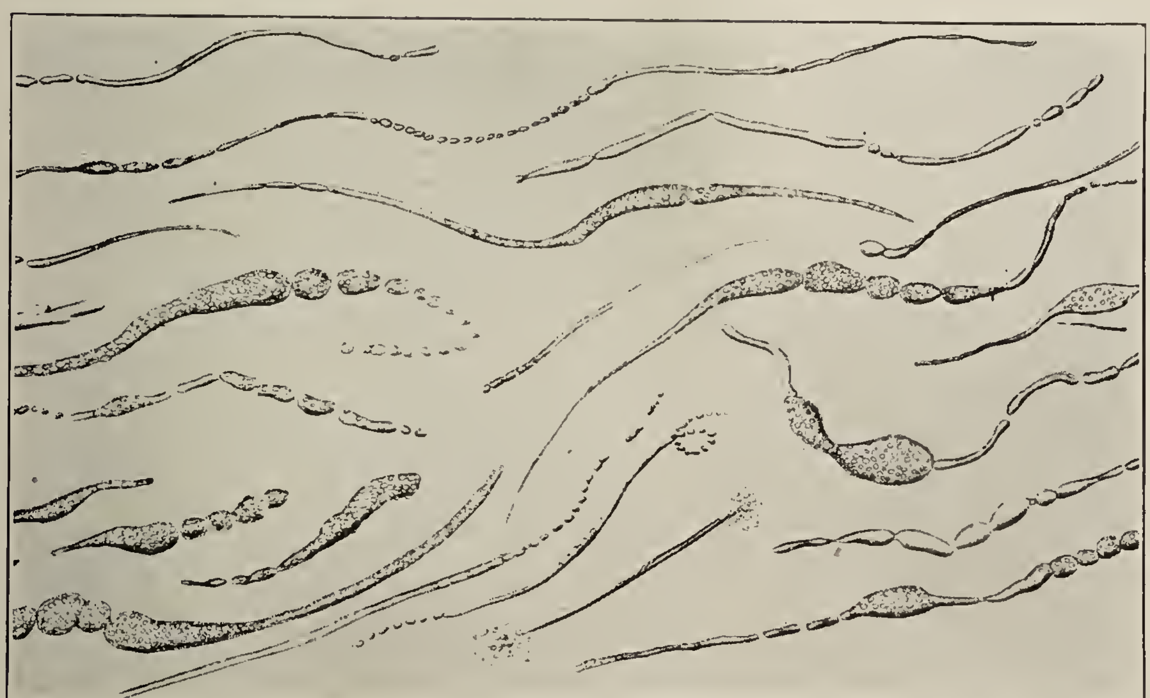

Fig. 45.

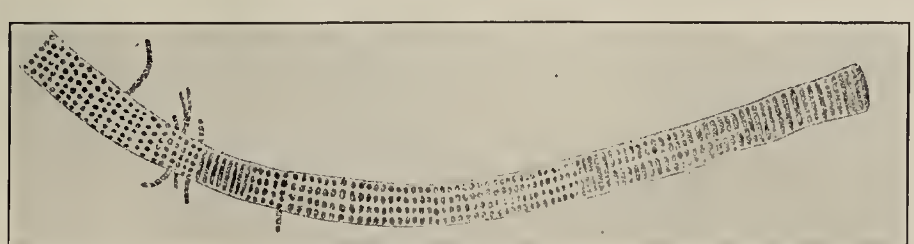

Fig. 46.

PLATE M.

FIG. 47 (p. 94).—*Crenothrix Kühniana*. *Zopf* (1883, original fig. 6). ×600.

48 (p. 94).—*Beggiatoa alba*. *Zopf* (1883, original fig. 27). ×900.

49 (p. 96).—*Vibrio cholerae*. *Hueppe* (1885, original fig. 2, p. 622).

50 (p. 96).—*Metabacterium polyspora* *Chatton* et *Pérard* (1913, p. 1233). ×2,000.

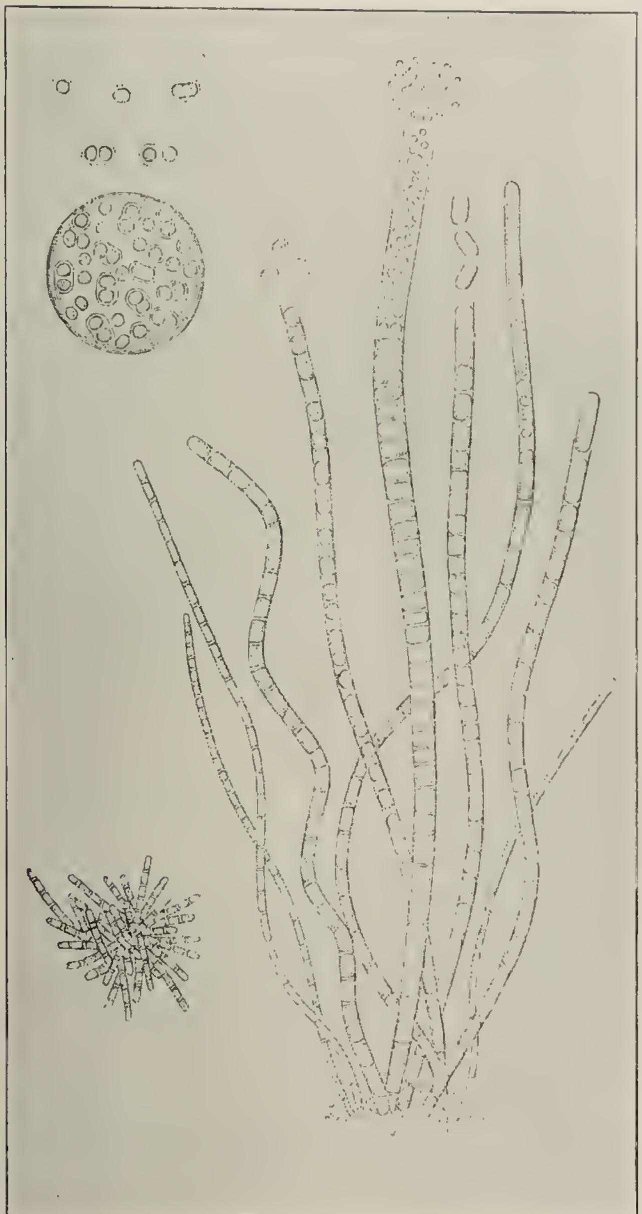

Fig. 47.

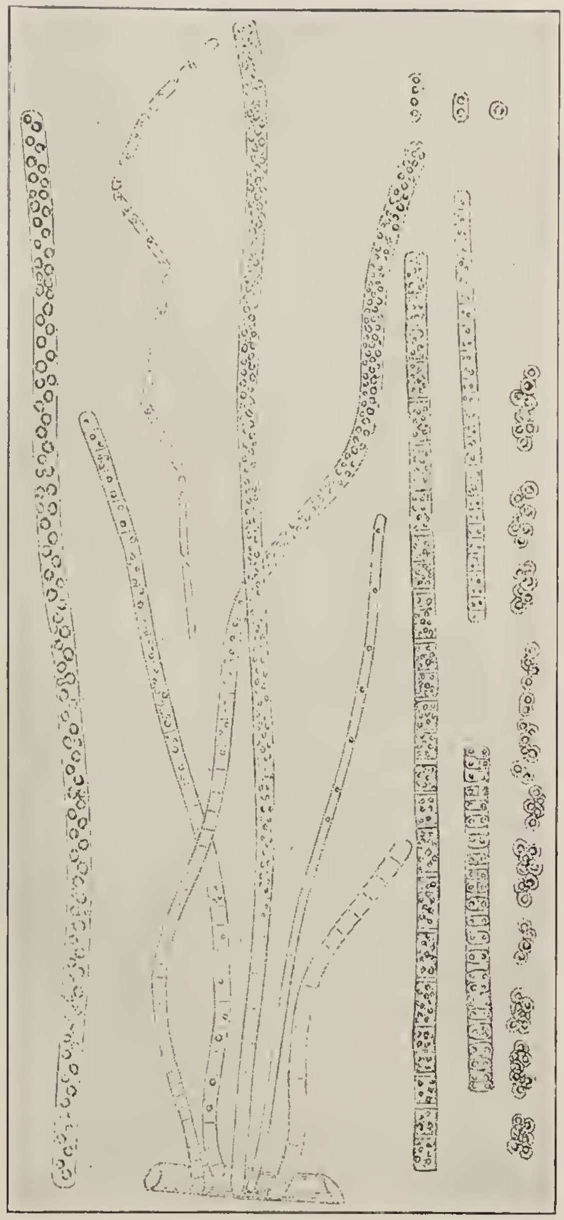

Fig. 48.

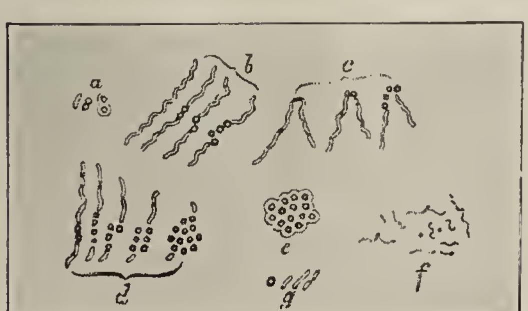

Fig. 49.

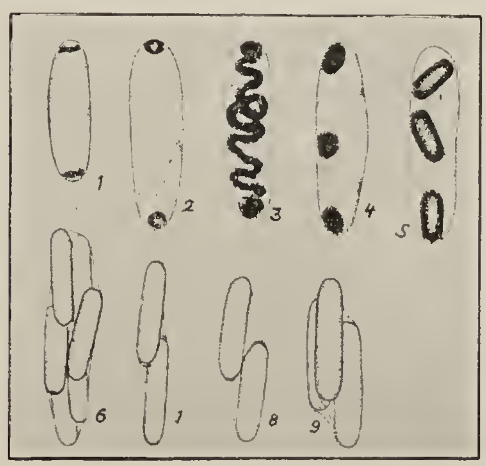

Fig. 50.

PLATE N.

FIG. 51 (p. 97).—*B. muralis.* *Tomaschek* (1888, p. 183). ×1,000.

52 (p. 98).—*Jodococcus vaginatus.* *W. Miller* (1889, original fig. 15, p. 54). ×1,100.

53 (p. 100).—*Ascobacterium luteum.* *Babes* (1895, original fig. 13 B). ×800.

54 (p. 101).—*B. typhi* and *V. cholerae* with "conidia." *Almquist* (1908, original figs. 5, 13, and 21).

55 (p. 102).—*B. tuberculosis.* *Crookshank* (1896, original fig. XI, 12). ×1,200.

56 (p. 102).—*Eubacillus multisporus Dangeard* (1891, original fig. VIII, 4). ×1,000.

57 (p. 103).—*Bact. oxydans.* *Henneberg* (1898, original fig. 1). ×1,000 (?).

Fig. 51.

Fig. 53.

Fig. 54.

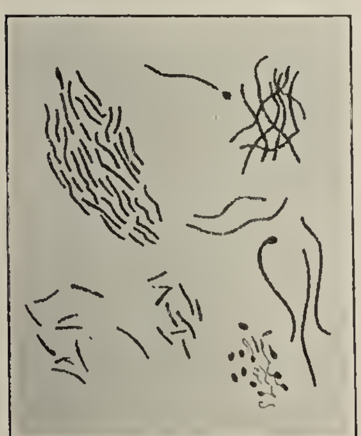

Fig. 55.

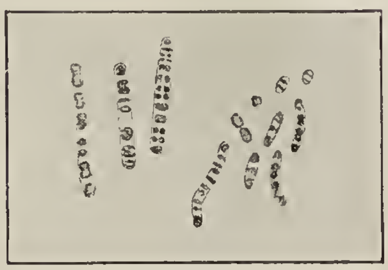

Fig. 52.

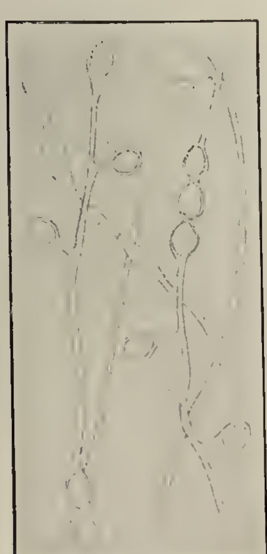

Fig. 56.

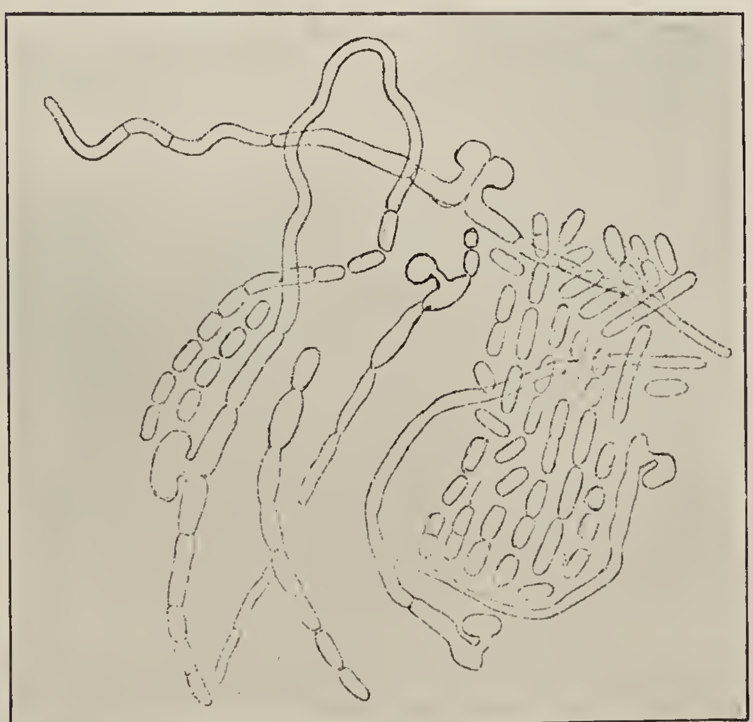

Fig. 57.

PLATE O.

FIG. 58 (p. 103).—Upgrowth of *B. pestis*. *N. K. Schultz* (1901 *a*, original fig. I). ×1,000.

59 (p. 106).—"Spore" formation by spirochaets. *Fantham* (1911, original fig. 5, p. 489).

60 (p. 106).—*Spirochaeta anodontae*. *Bosanquet* (1911, original figs. 21 and 22). ×2,000.

61 (p. 111).—Regeneration of *B. pestis*. *N. K. Schultz* (1901 *a*, original fig. II). ×1,000.

62 (p. 117).—"Plasmoptysis" of *V. cholerae*. *A. Fischer* (1903, original fig. 27). ×1,500.

63 (p 123).—*Saprospira grandis* (left) and *Cristispira tapetos* (right). *Gross* (1912, original figs. 8 and 9).

64 (p. 123).—Microcysts of *B. cohaerens* (×1,000) and of *B. ruminatus* (×3,500). *A. Meyer* (1901 *b*, original figs. XX, 4 and 15).

65 (p. 123).—*Myxococcus macrosporus*. *Zukal* (1897, original fig. 3). ×1,400.

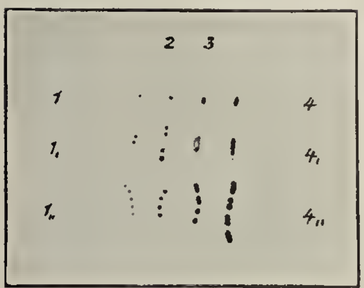

Fig. 58.

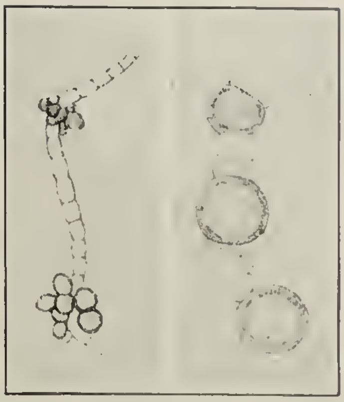

Fig. 64.

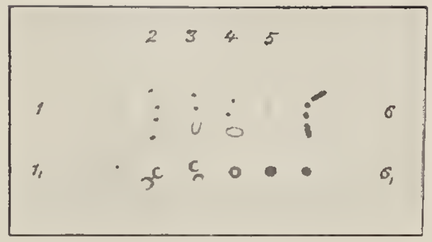

Fig. 61.

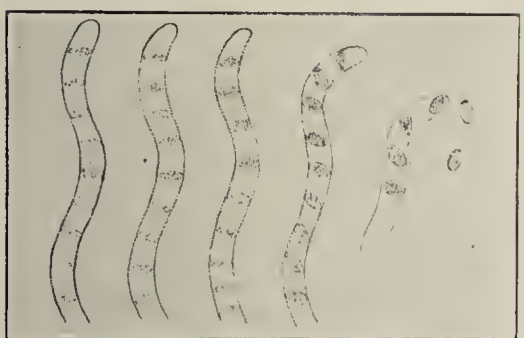

Fig. 59.

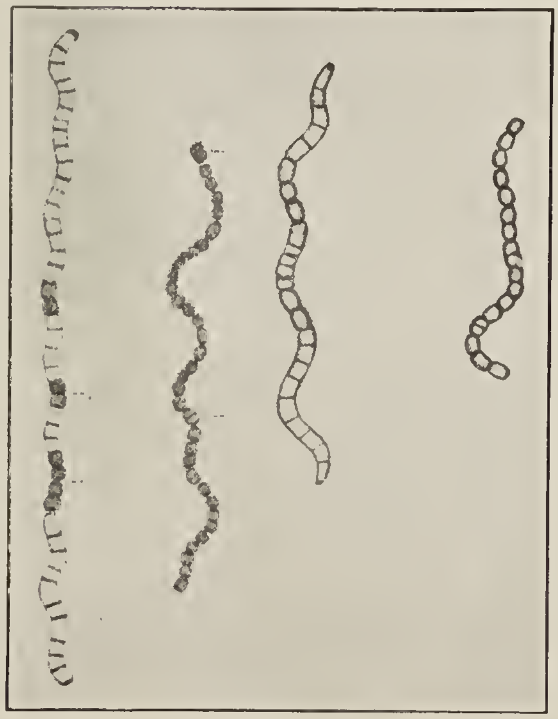

Fig. 63.

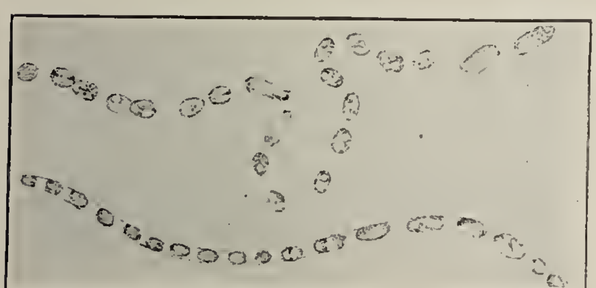

Fig. 60.

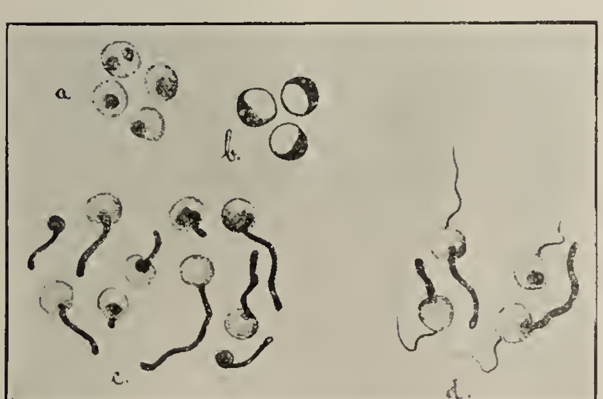

Fig. 62.

Fig. 65.

PLATE P.

FIG. 66 (p. 124).—Gonidia formation of *B. radicicola*. *Morck* (1891, original figs. III, 4, and V, 12).

67 (p. 125).—Gonidangia of *B. radicicola*. *Morck* (1891, original figs. III, 2 *b-d*).

68 (p. 125).—Gonidangia from diphtheria. *Letzerich* (1876, original figs. XII, 1–4). ×480.

69 (p. 128).—Crenothrix branching. *Migula* (1900, original fig. 43 *f* and *g*). ×1,000.

70 (p. 130).—Upgrowth of *Cladothrix dichotoma*. *Billet* (1890, original figs. IV, 4 and 5). ×1,600.

71 (p. 132).—*Spirochaeta icterohaemorrhagica* with regenerative bodies. *Inada, Ido, Hoki, Kaneko*, and *Ito* (1916, original figs. 40–47 on Pl. 61).

72 (p. 132).—*Streptococcus pyogenes*. *Hewlett* (1902. original fig. II*a*). ×1,500.

73 (p. 136).—*Spirobacillus Cienkowskii*. *Metchnikoff* (1889, original fig. 14, Pl. 1). ×2,020.

74 (p. 143).—Coiled spirochaets. *Prowazek* (1907*a*, original fig. I, 8*b*).

75 (p. 143).—Encysted spirochaets. *Inada* et al. (1916, original figs. 71 and 72).

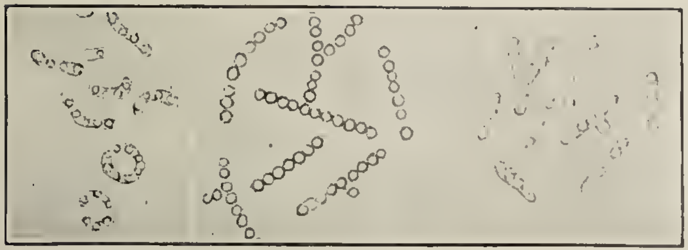

Fig. 66.

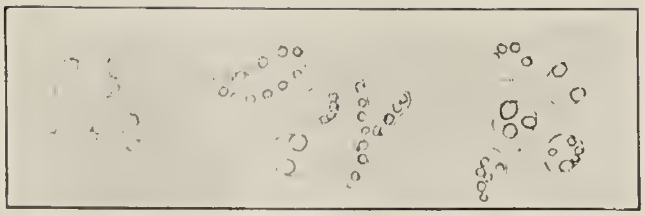

Fig. 67.

Fig. 68.

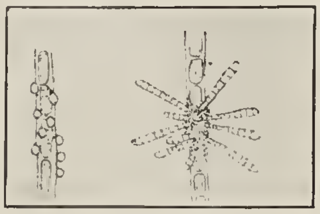

Fig. 69.

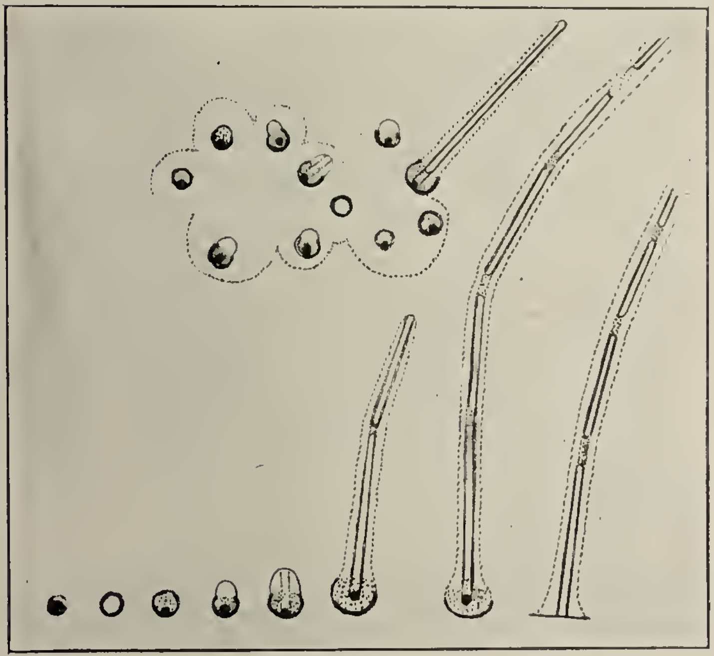

Fig. 70.

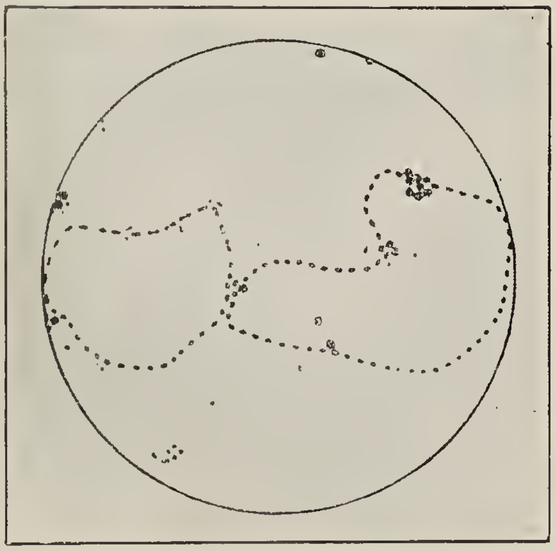

Fig. 72.

Fig. 71.

Fig. 73.

Fig. 74.

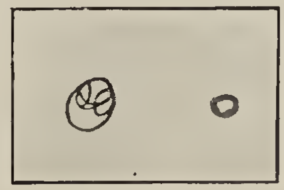

Fig. 75.

PLATE Q.

Fig. 76 (p. 148).—Bacterial development from "micro-gonidia." *Karsten* (1869, original fig. V).

77 (p. 148).—Rods and "microzymas." *Béchamp* (1883, original fig. I, 4). ×650.

78 (p. 167).—Development of protozoa and fungi. *Pineau* (1845 *a*, Pl. 4 bis). ×400. Figs. 8–10, *Monas lens;* 11–13, *Enchelys ovata;* 14–20, *Vorticella infusionum;* 21–27, *Penicillium glaucum.*

79 (p. 168).—Development of protozoa (*Podophyra* and *Actinophrys*). *Perty* (1852, original figs. VIII, 9 and 10). ×1,000.

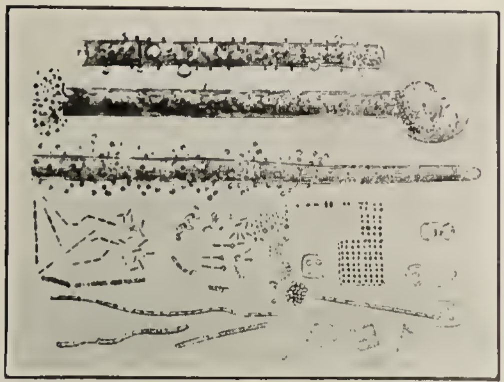

Fig. 76.

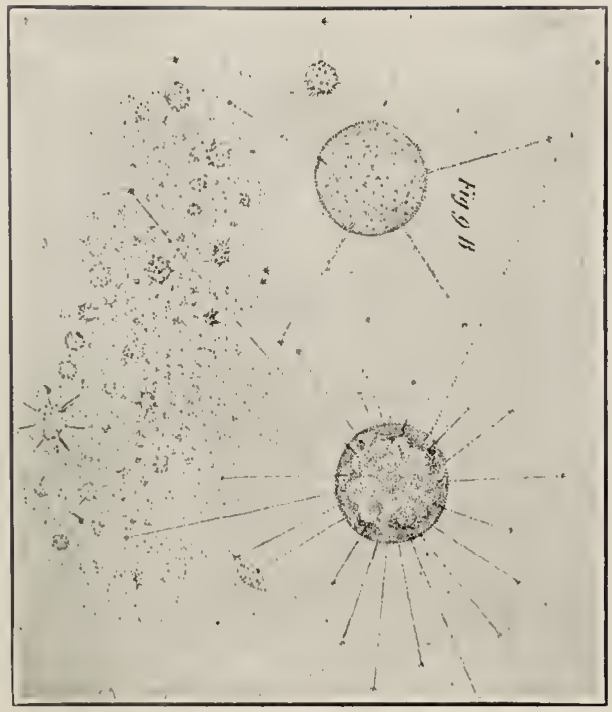

Fig. 79.

Fig. 77.

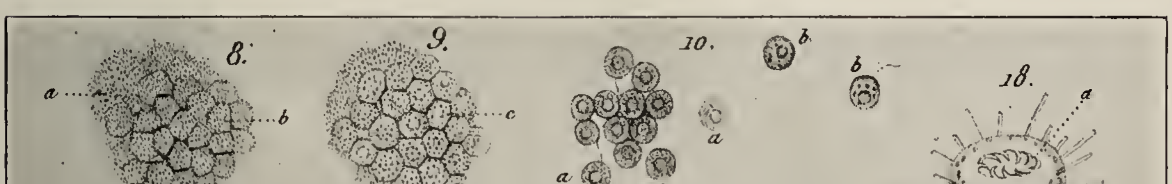

Fig. 78.

PLATE R.

FIG. 80 (p. 170).—Growth obtained from diphtheria. *Letzerich* (1876, original figs. XII, 5–10). ×480.

81 (p. 172).—Regeneration of yeast cells in vinegar. *Béchamp* (1883, original fig. I, 5). ×650.

82 (p. 173).—Symplasm from leprous tissue. *Lutz* (1886, original figs. 1–6). ×1,000.

83 (p. 174).—Growth of bacteria from root nodules. *Frank* (1890, original figs. VIII, 34 *a–c*). *a* and *b* ×660, *c* ×1,030.

Fig. 80.

Fig. 81.

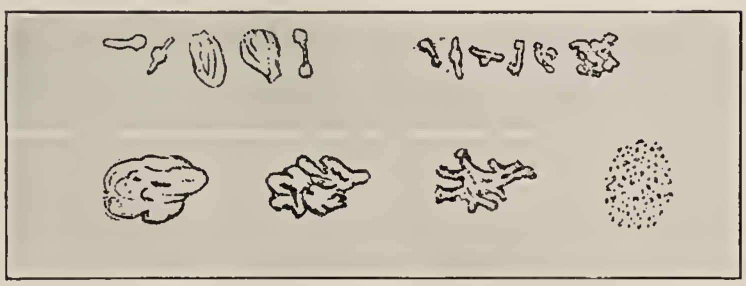

Fig. 82.

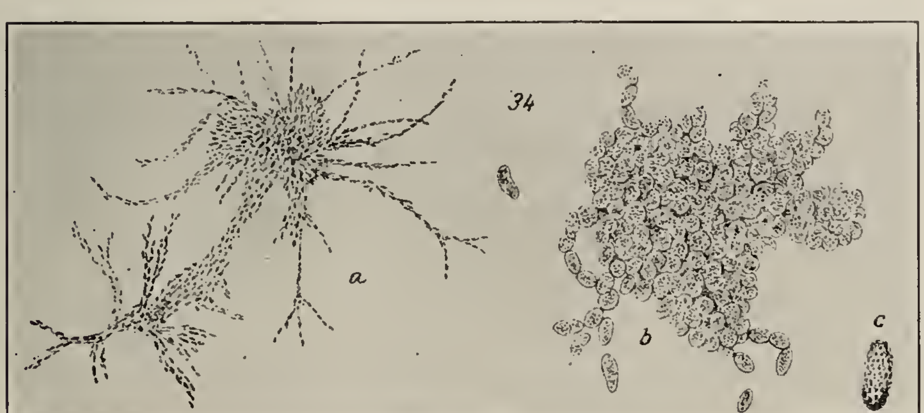

Fig. 83.

PLATE S.

FIG. 84 (p. 174).—Symplasm from root nodules. *Morck* (1891, originals figs. 3 and 12 *c* and *f*).

85 (p. 175).—Irregular cells of *B. cyanogenes*. *Neelsen* (1880, original fig. XI, 10). ×650.

86 (p. 177).—*Spirillum rubrum*. *Meirowsky* (1914 *b*, original figs. V *b*, 4–5). ×2,000.

87 (p. 180).—*Myxococcus ruber*. *Baur* (1905, original fig. 3, p. 113).

88 (p. 181).—Cyst of Polyangium. *Zukal* (1897, original fig. 8). ×50.

89 (p. 201).—*Spirochaeta gallinarum*. *Prowazek* (1906 *b*, original figs. II, 10 *c*, 11 *a* and *b*). ×1,560.

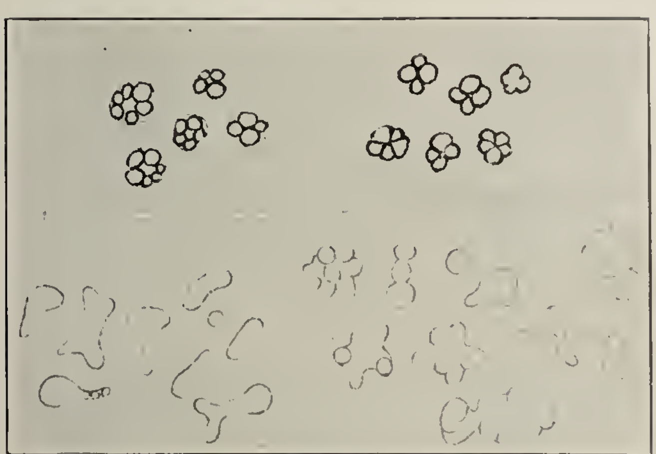

Fig. 84.

Fig. 85.

Fig. 86.

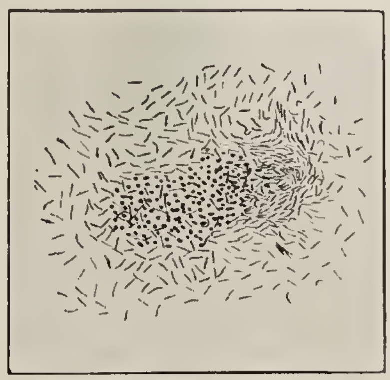

Fig. 87.

Fig. 88.

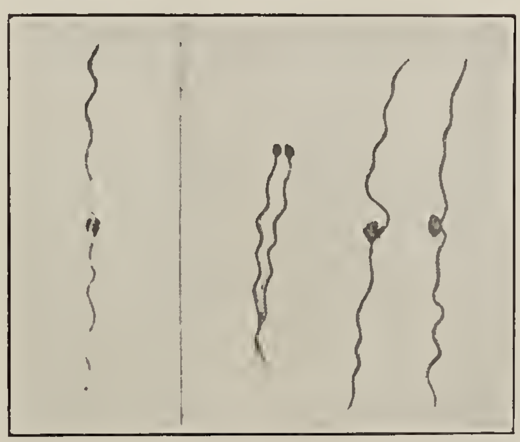

Fig. 89.

PLATE I.

Fig. 1. (p. 43): Microc. candicans. *Löhnis* and *Smith* (1916 *a*, original fig. 13). ×1,000.
2. (pp. 43, 135): Microc. candicans. *Löhnis* and *Smith* (1916 *a*, original fig. 37). ×1,000.
3. (pp. 43, 135): Microc. candicans. *Löhnis* and *Smith* (1916 *b*, original fig. 14). ×1,000.
4. (pp. 43, 135): Microc. candicans. *Löhnis* and *Smith* (1916 *b*, original fig. 15). ×1,000.
5. (pp. 43, 135): Microc. rubefaciens. *Matzuschita* (1900, original fig. 2). ×1,000.
6. (pp. 43, 135): Microc. flavus. *Matzuschita* (1900, original fig. 4). ×1,000.
7. (p. 44): Microc. melitensis. *Jordan* (1916, original fig. 99). ×1,000.
8. (pp. 44, 190: Microc. candicans. *Löhnis* and *Smith* (1916 *b*, original fig. 40). ×1,000.
9. (pp. 48, 191): Poliomyelitis. *Rosenow* and *Towne* (1917, original fig. X, 7*c*). ×1,000.
10. (p. 48): Poliomyelitis. *Mathers* (1917, original figs. I, 1 and 3). ×1,200.
11. (pp. 48, 142): Streptoc. lactis. *Löhnis* and *Smith* (1916 *b*, original fig. 10). ×1,000.
12. (p. 48): Streptoc. tyrogenus. *Migula* (1900, v. II, original fig. I, 2). ×1,000.

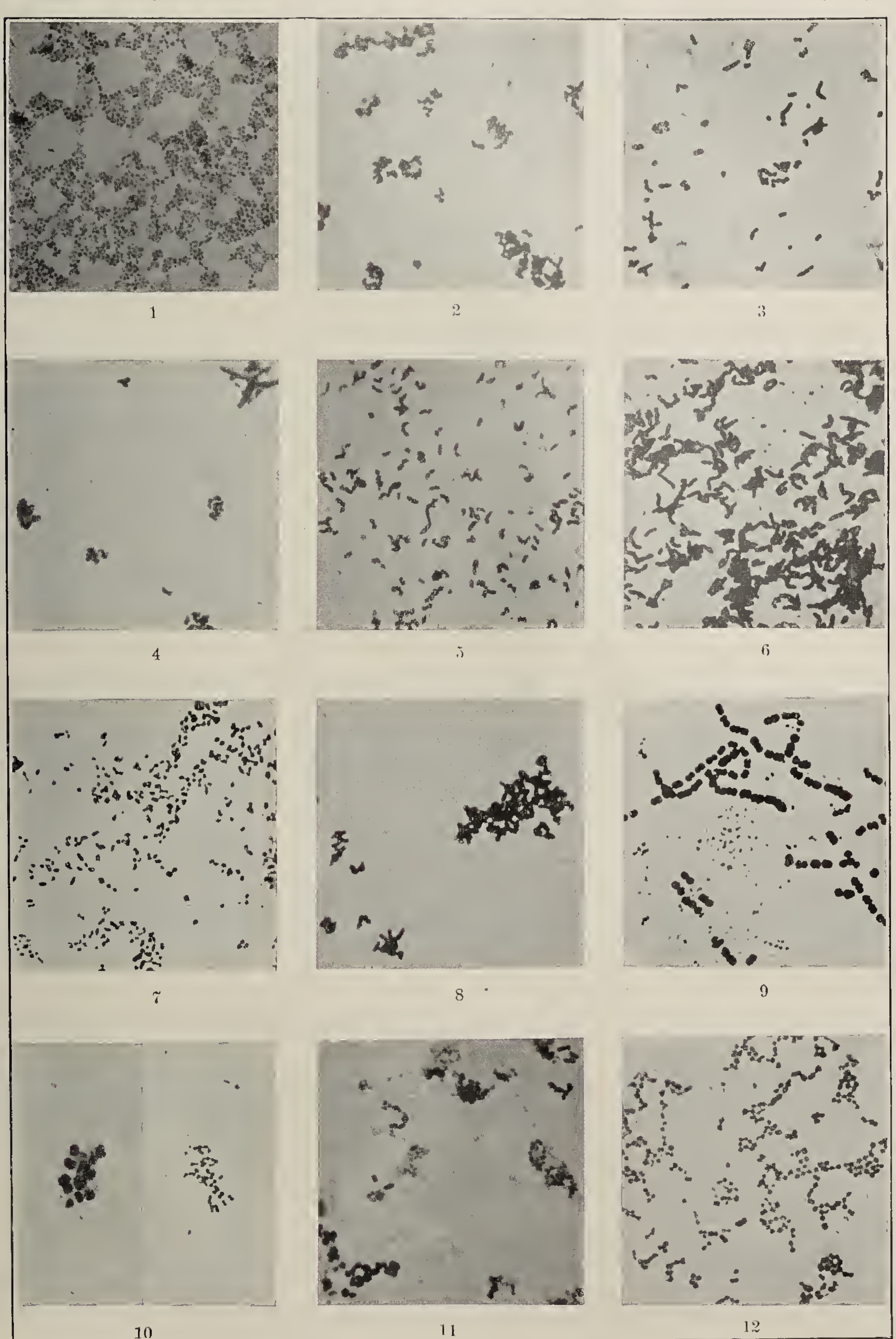
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PLATE II.

Fig. 13. (p. 48): Streptoc. equi. *Migula* (1900, v. II, original fig. II, 5). ×1,000.
14. (p. 48): Sarcina flava. *Löhnis* and *Smith* (1916 *b*, original fig. 11). ×1,000.
15. (pp. 48, 142): Sarc. flava. *Löhnis* and *Smith* (1916 *b*, original fig. 12). ×1,000.
16. (pp. 48, 190): Sarc. flava. *Löhnis* and *Smith* (1916 *b*, original fig. 54). ×1,000.
17. (pp. 48, 190): Sarc. flava. *Löhnis* and *Smith* (1916 *b*, original fig. 55). ×1,000.
18. (pp. 49, 134): Bact. bruneum. *Matzuschita* (1900, original fig. 6). ×1,000.
19. (p. 49): Azotob. vitreum. *Löhnis* and *Hanzawa* (1914, original fig. 24). ×800.
20. (p. 49): Azotob. vitreum. *Löhnis* and *Hanzawa* (1914, original fig. 22). ×800.
21. (p. 49): Azotob. vitreum. *Löhnis* and *Hanzawa* (1914, original fig. 23). ×800.
22. (pp. 52, 192): Typhus exanthematicus. *P. Th. Müller* (1913, original fig. 2). ×1,000.
23. (p. 52): Typhus exanthematicus. *P. Th. Müller* (1913, original fig. 5). ×1,000.
24. (pp. 52, 193): Typhus exanthematicus. *P. Th. Müller* (1913, original fig. 1). ×1,000.

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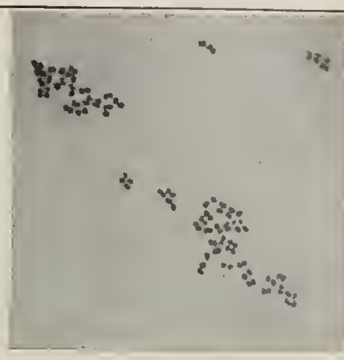

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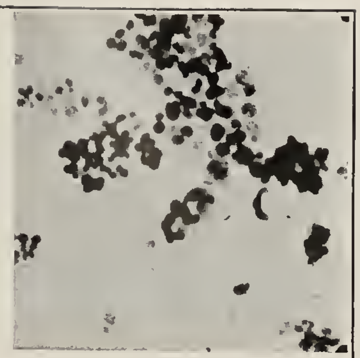

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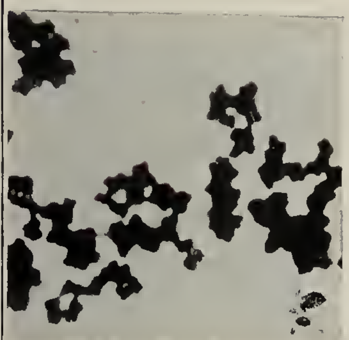

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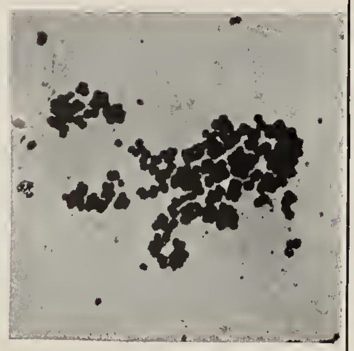

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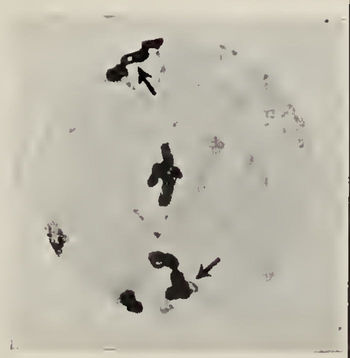

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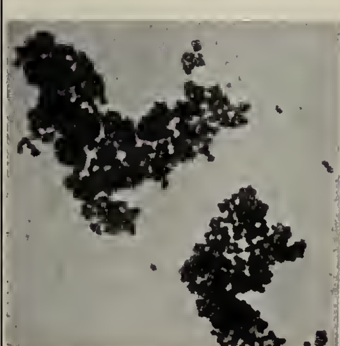

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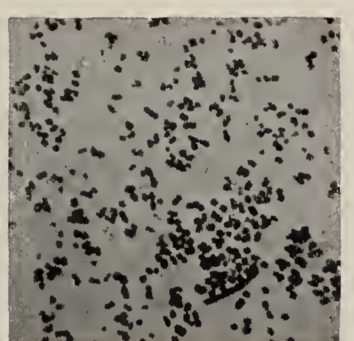

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PLATE III.

Fig. 25. (p. 53): B. erysipelatos suum. *Itzerott* und *Niemann* (1895, original fig. 40). ×1,000.
26. (p. 52): B. erysipeloides. *Rosenbach* (1909, original fig. XIII, 5). ×1,000
27. (p. 52): B. erysipeloides. *Rosenbach* (1909, original fig. XII, 5). ×1,000.
28. (p. 53): B. murisepticum. *Rosenbach* (1909, original fig. XIII, 3). ×1,000.
29. (pp. 53, 192): B. erysipeloides. *Rosenbach* (1909, original fig. XII, 3). ×1,000.
30. (pp. 53, 134): B. cholerae gallinarum. *Itzerott* und *Niemann* (1895, original fig. 36). ×1,000.
31. (pp. 54, 101): B. pestis. *Muir* and *Ritchie* (1903, original fig. 148). ×1,000.
32. (p. 54): B. pestis. *Muir* and *Ritchie* (1903, original fig. 150). ×1,000.
33. (p. 54): B. pestis. *Muir* and *Ritchie* (1903, original fig. 147). ×1,000.
34. (pp. 54, 192): B. pestis. *Rowland* (1914, original fig. XIX, 12). ×1,000.
35. (pp. 54, 134): B. pestis. *Rowland* (1914, original fig. XXI, 17). ×1,000.
36. (pp. 56, 127): B. coli. *Matzuschita* (1900, original fig. 14). ×1,000.

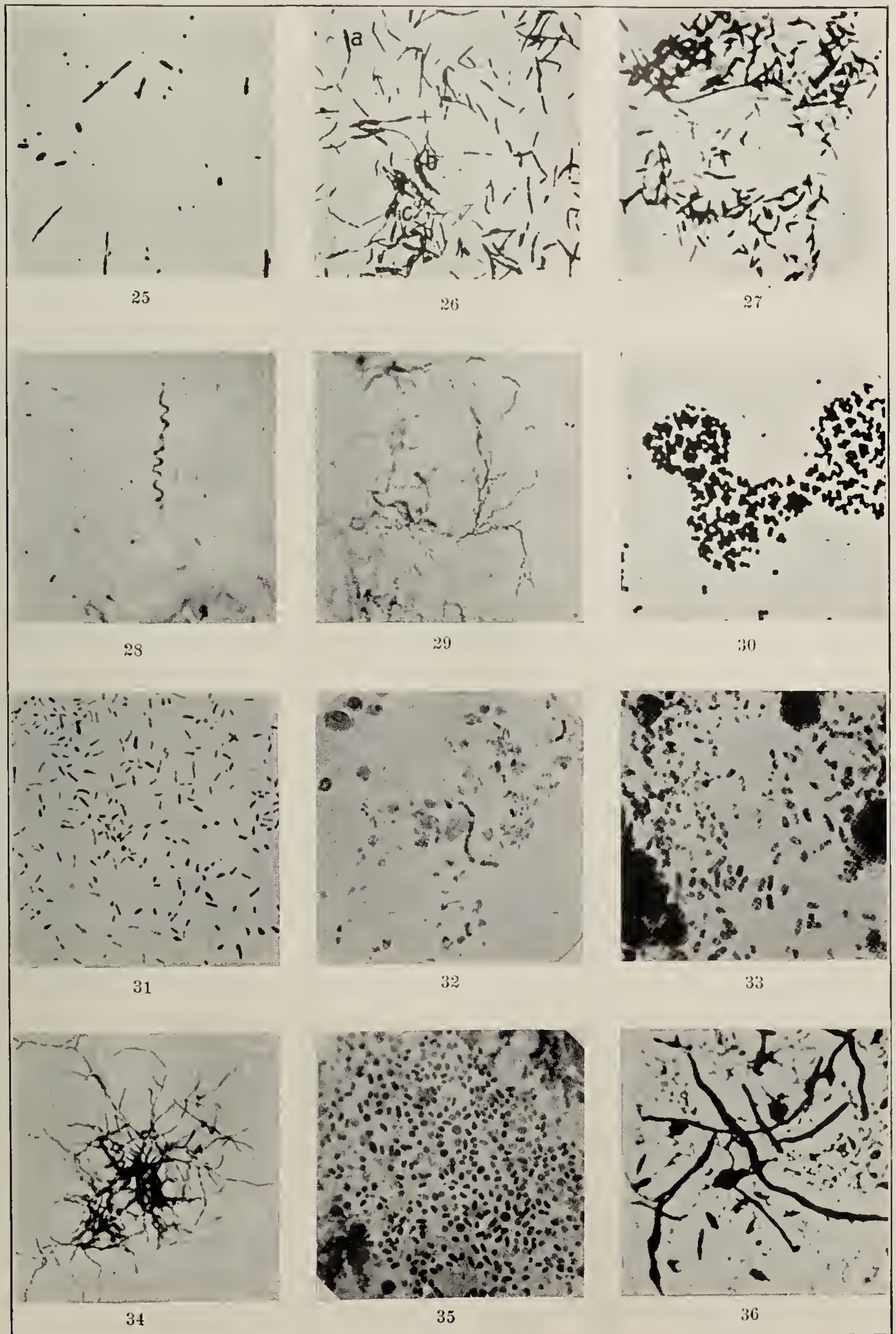
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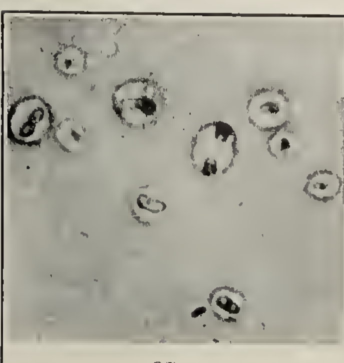
PLATE IV.

Fig. 37. (pp. 55, 185): B. pneumoniae. *Toenniessen* (1913, original fig. III). ×1,000.
38. (pp. 55, 185): B. pneumoniae. *Toenniessen* (1913, original fig. IV). ×1,000.
39. (pp. 55, 185): B. pneumoniae. *Toenniessen* (1913, original fig. V). ×1,000.
40. (pp. 55, 185): B. pneumoniae. *Toenniessen* (1913, original fig. VI). ×1,000.
41. (pp. 55, 185): B. pneumoniae. *Toenniessen* (1913, original fig. VII). ×1,000.
42. (pp. 55, 185): B. pneumoniae. *Toenniessen* (1913, original fig. VIII). ×1,000.
43. (p. 57): B. coli. *Kellerman* and *Scales* (1916, original fig. 8). ×1,000.
44. (pp. 57, 177): B. coli. *Kellerman* and *Scales* (1916, original fig. 11/12). ×1,000.
45. (pp. 57, 177): B. coli. *Kellerman* and *Scales* (1916, original fig. 9). ×1,000.
46. (p. 57): B. typhi. *Matzuschita* (1900, original fig. 16). ×1,000.
47. (p. 57): B. typhi. *Itzerott* und *Niemann* (1895, original fig. 18). ×1,000.
48. (p. 60): B. fluorescens. *Löhnis* and *Smith* (1916 *b*, original fig. 7). ×1,000.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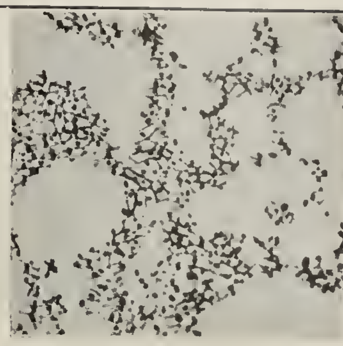
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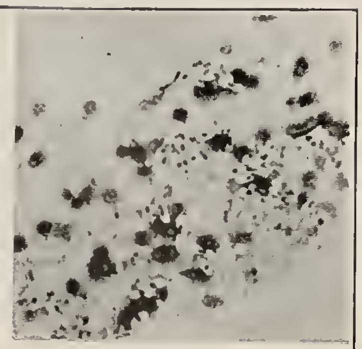
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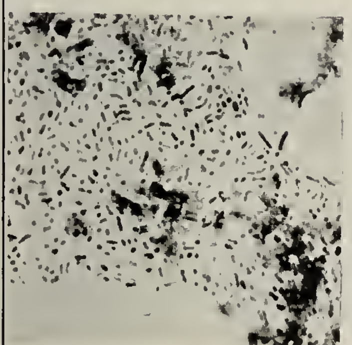
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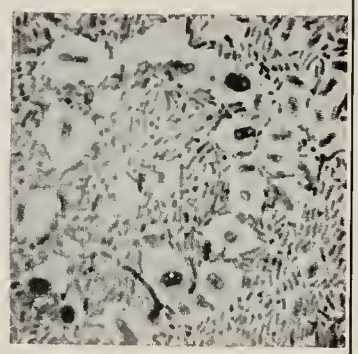
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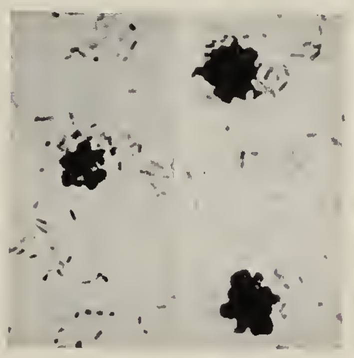
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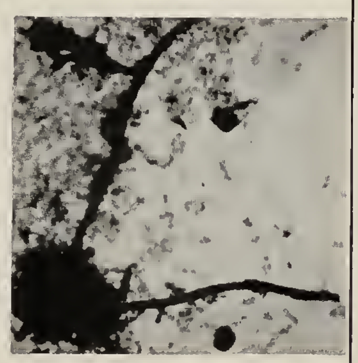
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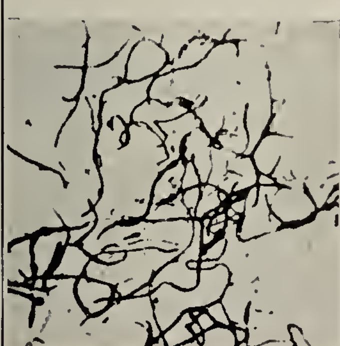
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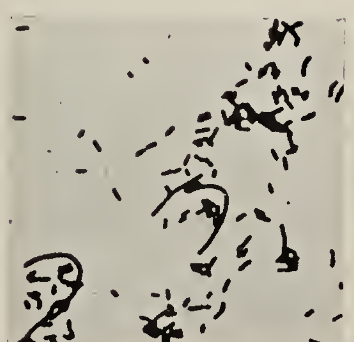
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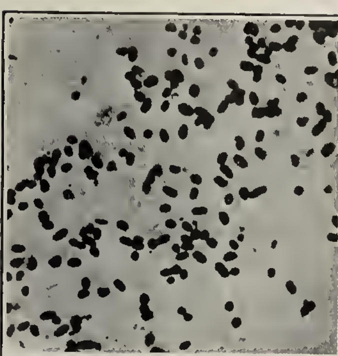
PLATE V.

FIG. 49. (p. 61): Nitrosomonas Zürich. *Winogradsky* (1892, original fig. 1). ×1,000.
50. (p. 61): Nitrosomonas Kasan. *Winogradsky* (1892, original fig. 4). ×1,000.
51. (p. 61): Nitrosomonas Java. *Winogradsky* (1892, original fig. 12). ×1,000.
52. (p. 61): Nitrobacter. *Winogradsky* (1891, original fig. XVIII, 1). ×1,000.
53. (p. 61): Nitrobacter. *Winogradsky* (1892, original fig. 16). ×1,000.
54. (p. 63): B. anthracis. *Itzerott* und *Niemann* (1895, original fig. 13). ×1,000.
55. (p. 63): B. anthracis. *Itzerott* und *Niemann* (1895, original fig. 14). ×1,000.
56. (p. 63): B. anthracis. *Itzerott* und *Niemann* (1895, original fig. 15). ×1,000.
57. (pp. 63, 138): B. anthracis. *Matzuschita* (1900, original fig. 31). ×1,000.
58. (p. 63): B. anthracis. *Henri* (1914, original fig. 4). ×925.
59. (pp. 63, 134): B. anthracis. *Henri* (1914, original fig. 5). ×925.
60. (p. 63): B. anthracis. *Henri* (1914, original fig. 6). ×925



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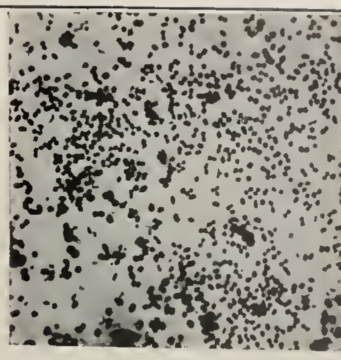

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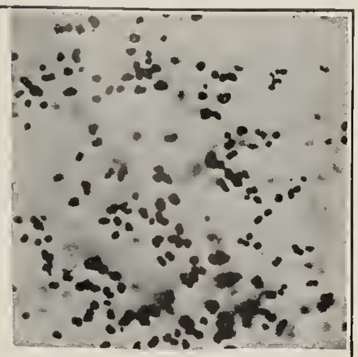

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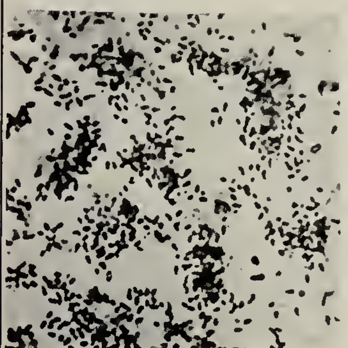

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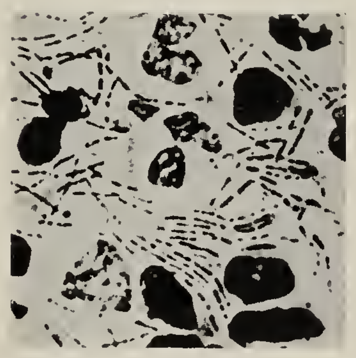

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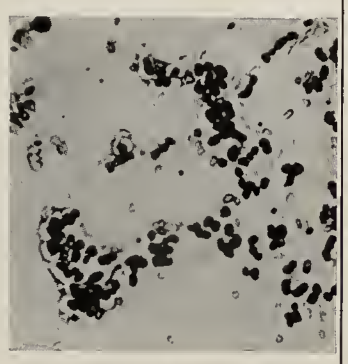

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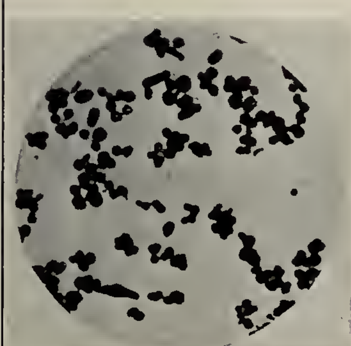

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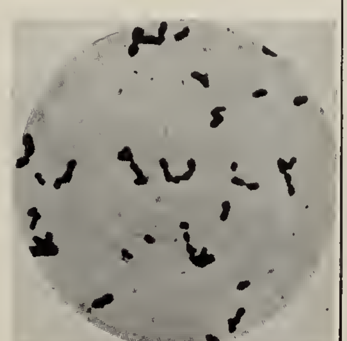

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PLATE VI.

Fig. 61. (p. 64): B. anthracis. *Henri* (1914, original fig. 7). ×925.
62. (p. 64): B. anthracis. *Henri* (1914, original fig. 8). ×925.
63. (p. 64): B. anthracis. *Henri* (1914, original fig. 9). ×925.
64. (p. 64): B. subtilis. *Löhnis* and *Smith* (1916 *b*, original fig. 6). ×1,000.
65. (pp. 64, 138): B. subtilis. *Löhnis* and *Smith* (1916*a*, original fig. 26). ×1,000.
66. (p. 64): Bac. aus Hackfleisch. *Maassen* (1904, original fig. XIV, 11). ×1,000.
67. (p. 65): B. malabarensis. *Löhnis* and *Pillai* (1907, original fig. 2). ×1,200.
68. (pp. 65, 134): B. Azotobacter. *Löhnis* and *Hanzawa* (1914, original fig. 28). ×800.
69. (pp. 65, 136): B. Azotobacter. *Löhnis* and *Smith* (1916 *a* original fig. 20). ×1,000.
70. (pp. 65, 185): B. Azotobacter. *Löhnis* and *Smith* (1916 *a* original fig. 16). ×1,000.
71. (p. 65): Azotobacter. *Walton* (1915, original fig. I, 9). ×1,000.
72. (p. 65): Azotobacter. *Walton* (1915, original fig. I, 10). ×1,000.

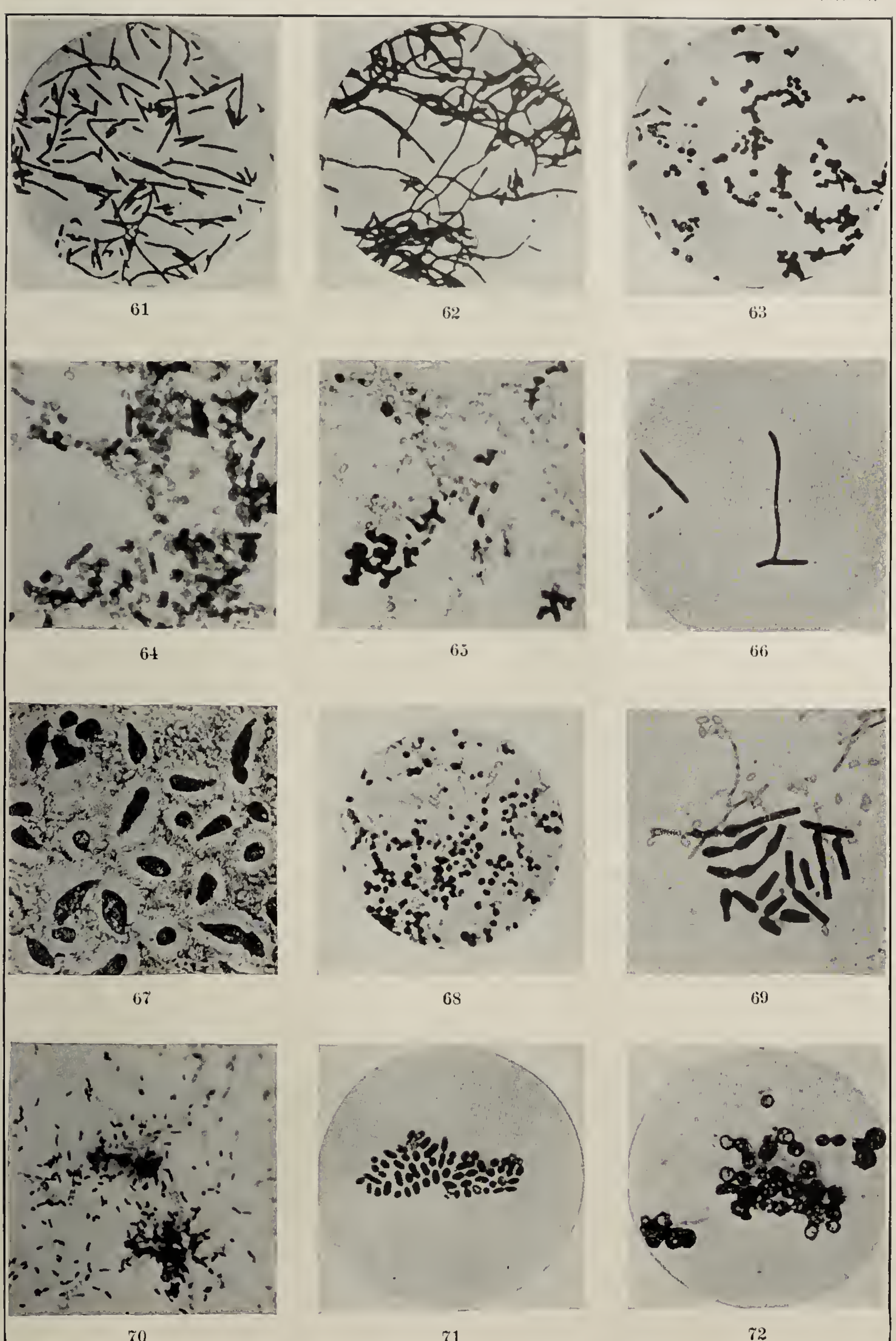

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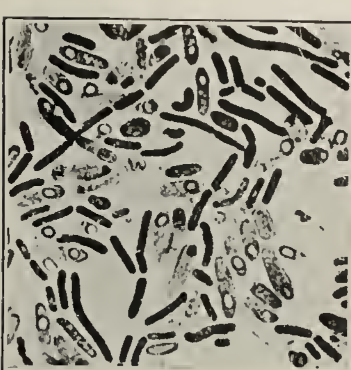
PLATE VII.

FIG. 73. (p. 66): Clostr. Pastorianum. *Winogradsky* (1902, original fig. 3). ×1,000.
74. (p. 67): B. Chauvoei. *Grassberger* (1903, original fig. 54). ×1,000.
75. (p. 67): B. Chauvoei. *Grassberger* (1903, original fig. 21). ×1,000.
76. (p. 67): B. Chauvoei. *Hibler* (1908, original fig. X, 16). ×800(?).
77. (p. 67): B. Chauvoei. *Hibler* (1908, original fig. XVI, 7). ×1,000(?).
78. (p. 67): B. oedematis maligni. *Grassberger* (1903, original fig. 42). ×1,000.
79. (p. 69): V. cholerae. *Fraenkel* und *Pfeiffer* (1895, original fig. 99). ×1,000.
80. (p. 69): V. cholerae. *Itzerott* und *Niemann* (1895, original fig. 53). ×1,000.
81. (p. 70): V. cholerae. *Stamm* (1914, original fig. XI, 2 and 4). ×1,000.
82. (p. 70): V. cholerae. *Stamm* (1914, original fig. XI, 5 and XII, 15). ×1,000.
83. (p. 70): V. cholerae. *Stamm* (1914, original figs. 1 and 2). ×1,000.
84. (p. 72): V. phosphorescens. *Maassen* (1904, original figs. 10 and 3). ×1,000.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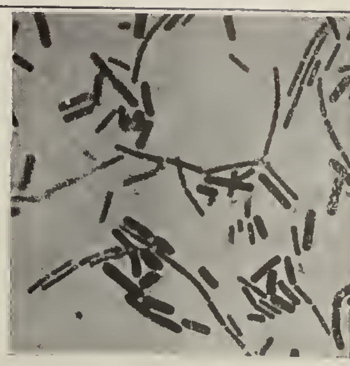
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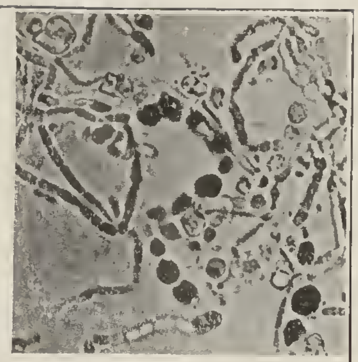
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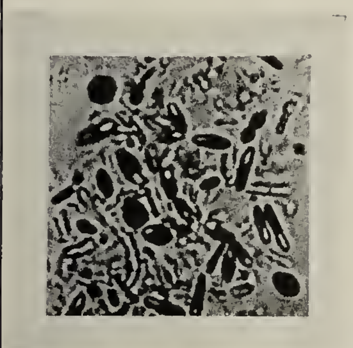
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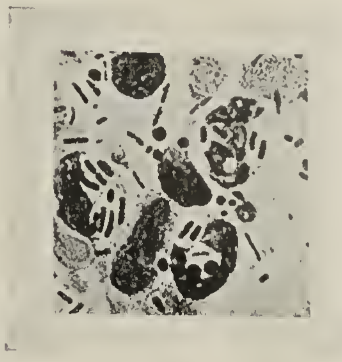
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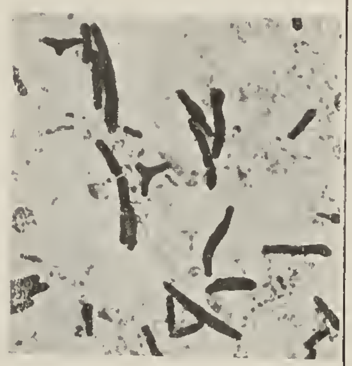
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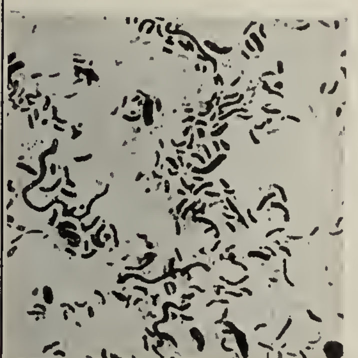
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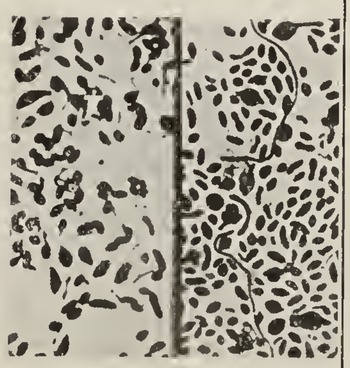
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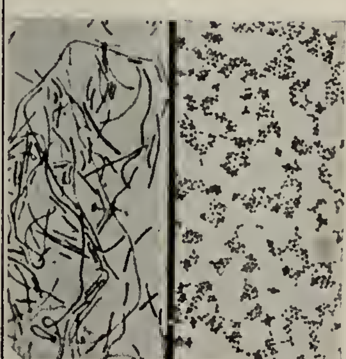
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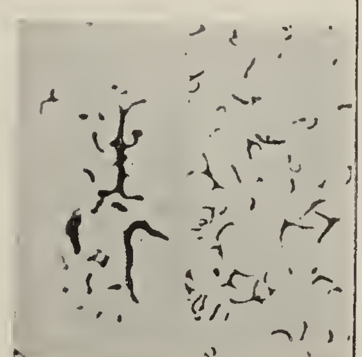
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PLATE VIII.

FIG. 85. (p. 72): V. lingualis. *Bajardi* (1903, original fig. 1). ×1,000.
86. (pp. 72, 203): Spirillum rubrum. *Reichenbach* (1901, original fig. 6). ×1,000.
87. (pp. 73, 203): Spirillum rubrum. *Reichenbach* (1901, original fig. 8/9). ×1,000.
88. (p. 73): Spirochaeta pallida. *Meirowsky* (1914 *b*, original fig. XI, 46, 55, and 56). ×2,000-3,000.
89. (pp. 76, 98): Streptothrix cuniculi. *Schmorl* (1891, original fig. 2). ×1,000.
90. (pp. 76, 98): Streptothrix cuniculi. *Schmorl* (1891, original fig. 5). ×1,000.
91. (pp. 77, 134): B. mallei. *Carpano* (1913, original fig. 1). ×1,000.
92. (p. 77): B. mallei. *Carpano* (1913, original fig. 2). ×1,000.
93. (p. 77): B. mallei. *Carpano* (1913, original fig. 3). ×1,000.
94. (p. 77): B. mallei. *Carpano* (1913, original fig. 4). ×1,000.
95. (p. 77): B. mallei. *Carpano* (1913, original fig. 5). ×1,000.
96. (pp. 77, 126): B. mallei. *Carpano* (1913, original fig. 6). ×1,000.

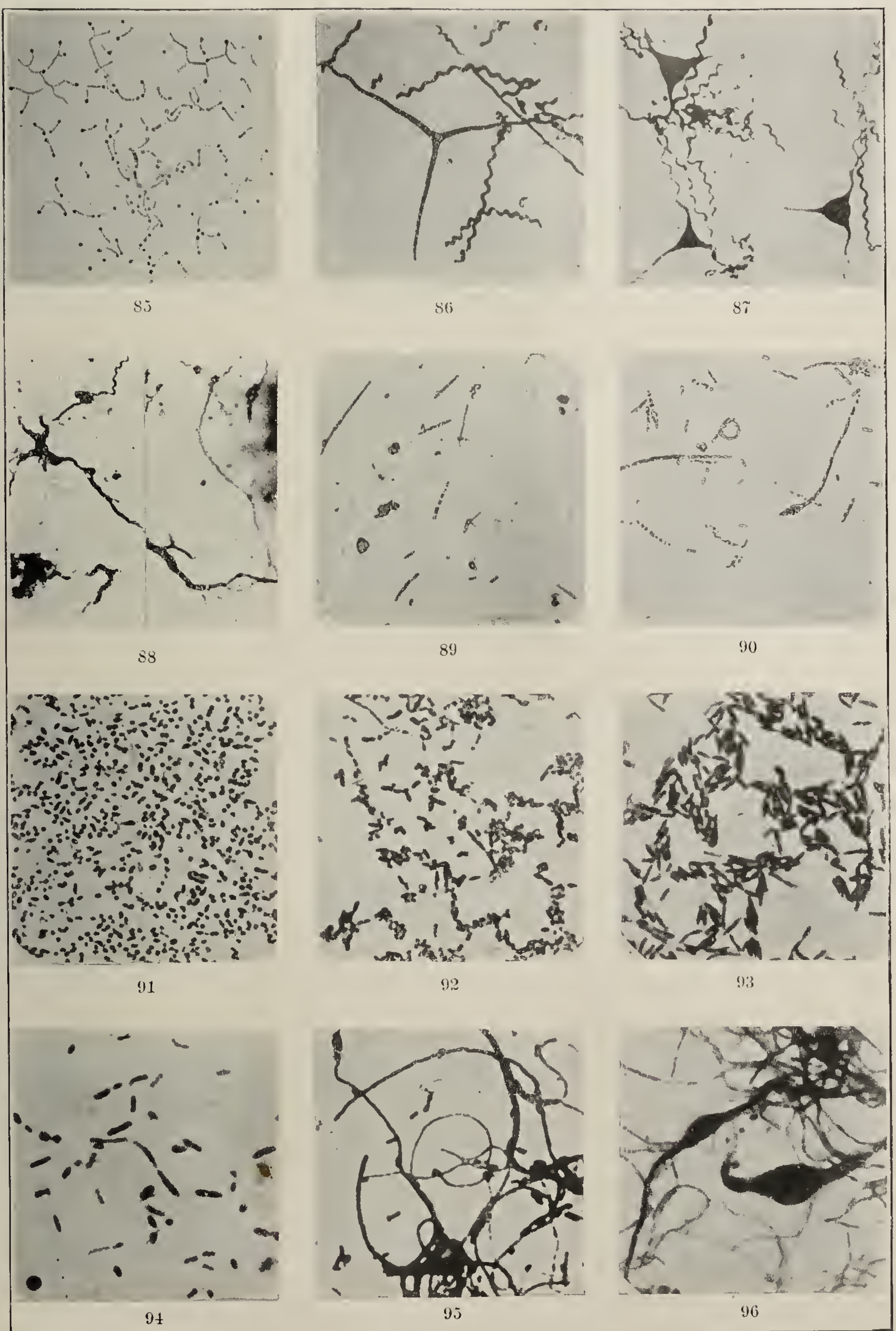
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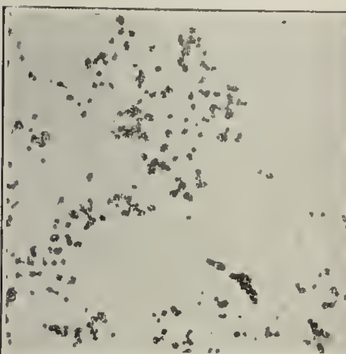
PLATE IX.

FIG. 97. (pp. 79, 134): B. diphtheriae. *J. Dale* (1910, original fig. 6). ×1,000.
98. (pp. 80, 134): B. variabilis. *Nakanishi* (1900 *e*, original fig. 8). ×1,000.
99. (p. 81): Corynebacterium. *E. de Negri* (1916, original fig. 12). ×560.
100. (p. 81): Corynebacterium. *E. de Negri* (1916, original fig. 11). ×560.
101. (pp. 81, 134): Corynebacterium. *E. de Negri* (1916, original fig. 30/73). ×560.
102. (pp. 84, 98): Pia mater tubercul. *Cornil* et *Babes* (1890, original fig. 342). ×500.
103. (pp. 84, 134): Tuberculosis. *Arrigo* (1900, original fig. 1 *a*). ×670.
104. (pp. 84, 134): Tuberculosis. *Arrigo* (1900, original fig. 2 *b*). ×670.
105. (p. 84): B. tuberculosis. *Migula* (1900, v. II, original fig. V, 3). ×1,000.
106. (p. 86): Pseudo-tuberculosis. *Preisz* (1894, original fig. III/IV). ×1,000.
107. (p. 86): Pseudo-tuberculosis. *Preisz* (1894, original fig. V). ×1,000.
108. (p. 86): Actinomyces. *J. Israël* (1878, original fig. II, 4). ×750.



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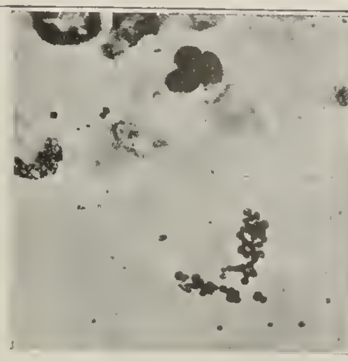

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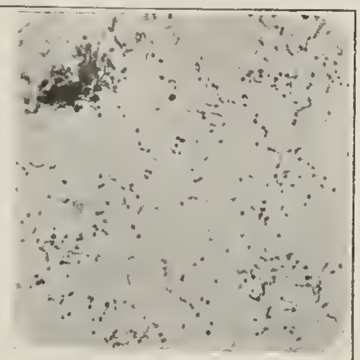

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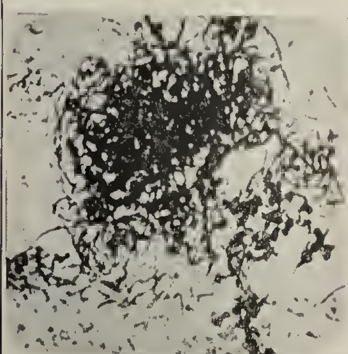

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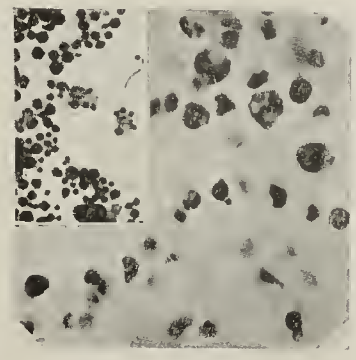

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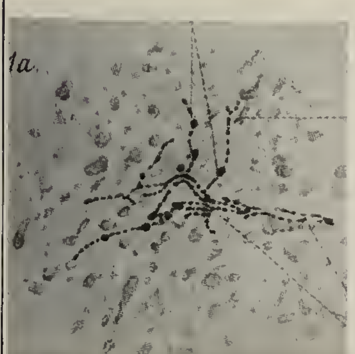

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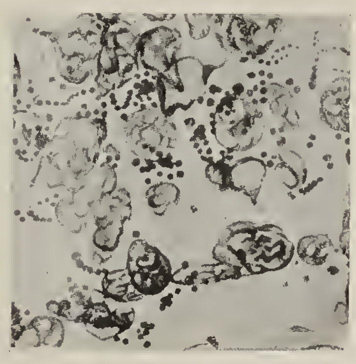

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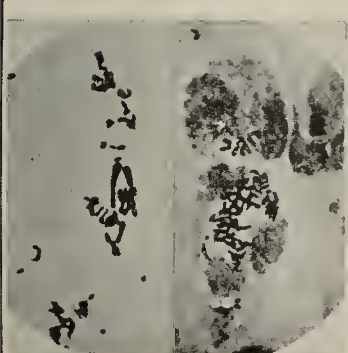

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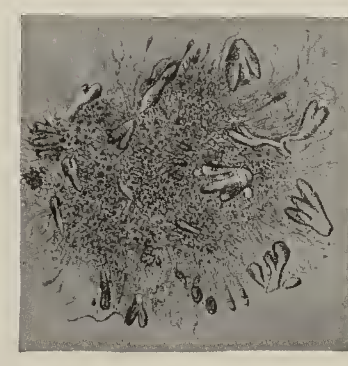

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PLATE X.

Fig. 109. (p. 92): B. termo. *R. Koch* (1877, original fig. XV, 4). ×500.
110. (p. 92): B. fluorescens. *Löhnis* and *Smith* (1916 *a*, original fig. 40). ×1,000.
111. (p. 92): B. anthracis. *R. Koch* (1877, original fig. XVI, 5). ×700.
112. (p. 92): B. anthracis. *Günther* (1906, original fig. 29). ×1,000.
113. (p. 94): B. anthracis. *R. Koch* (1881, original fig. VI, 33). ×700.
114. (p. 94): B. oedematis maligni. *R. Koch* (1881, original fig. VIII, 46). ×700.
115. (pp. 95, 126): B. Chauvoei. *Hibler* (1908, original fig. VIII, 18). ×1,900.
116. (pp. 95, 126): B. Chauvoei. *Hibler* (1908, original fig. VIII, 17). ×2,000.
117. (pp. 99, 138): B. Chauvoei. *Fraenkel* und *Pfeiffer* (1895, original fig. 60). ×1,000.
118. (pp. 99, 138): B. pestis. *Maassen* (1904, original fig. X, 4). ×1,000.
119. (pp. 99, 138): B. lact. aërogenes. *Maassen* (1904, original fig. X, 7). ×1,000.
120. (pp. 97, 138): Proteus vulgaris. *Hauser* (1885, original fig. X, 16). ×1,000.
121. (pp. 99, 138): V. cholerae. *Maassen* (1904, original fig. XI, 1). ×1,000.
122. (pp. 96, 126): Pneumococcus. *Artigalas* (1885, original fig. 1, pl. 5).
123. (pp. 97, 153): Proteus hominis capsulatus. *Bordoni-Uffreduzzi* (1888 *b*, original fig. VIII, 6). ×750.
124. (p. 98): V. cholerae. *Cornil* et *Babes* (1890, original fig. 275). ×1,500.
125. (p. 99): B. pyocyaneus. *Matzuschita* (1900, original fig. 26). ×1,000.
126. (p. 99): Spirilla. *Itzerott* und *Niemann* (1895, original fig. II, 7). ×1,000.
127. (p. 99): B. anthracis. *Itzerott* und *Niemann* (1895, original fig. III, 16). ×1,000.
128. (p. 99): B. capsulatus. *Itzerott* und *Niemann* (1895, original fig. VIII, 46). ×1,000.
129. (p. 99): V. Bonhoff. *Itzerott* und *Niemann* (1895, original fig. X, 60). ×1,000.

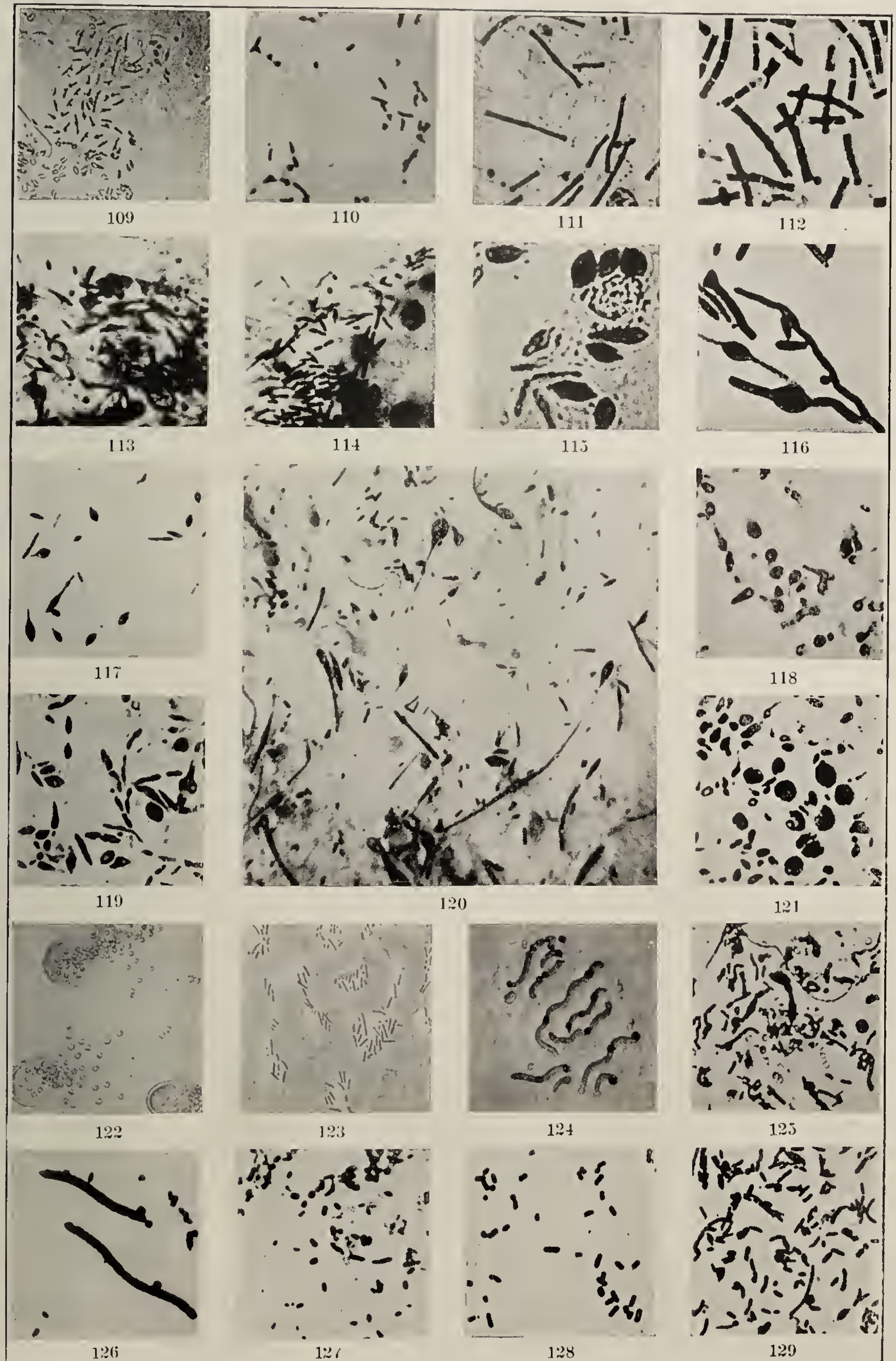
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PLATE XI.

FIG. 130. (p. 99): Spirillum rubrum. *Itzerott* und *Niemann* (1895, original fig. XVIII, 104). ×1,000.
131. (p. 99): Bacillus sp. *Zettnow* (1891, original fig. 14). ×1,650.
132. (p. 99): Spirillum Undula. *Zettnow* (1896, original fig. 16). ×1,125.
133. (p. 100): Spirillum sp. *Migula* (1904, original fig. II, 8). ×1,000.
134. (p. 100): B. proteus. *Migula* (1904, original fig. II, 4). ×1,000.
135. (pp. 101, 202): B. typhi. *Almquist* (1916, original fig. 4). ×1,000.
136. (p. 101): B. typhi. *Almquist* (1916, original fig. 5). ×1,000.
137. (p. 101): B. dysenteriae. *Almquist* (1916, original fig. 23). ×1,000.
138. (pp. 101, 202): B. typhi. *Almquist* (1917, original fig. 1). ×1,000.
139. (pp. 101, 202): V. cholerae. *Almquist* (1917, original fig. 4). ×1,000.
140. (pp. 101, 202): V. cholerae. *Friedrich* (1892, original fig. V, 4). ×800.
141. (p. 101): B. pyocyaneus. *Muir* and *Ritchie* (1903, original fig. 69). ×1,000.
142. (p. 101): B. enterititidis. *Günther* (1906, original fig. 54). ×1,000.
143. (p. 101): B. ochraceus. *Migula* (1900, original fig. XI, 3). ×1,000.
144. (p. 101): Spirillum sporiferum. *Migula* (1900, original fig. XVII, 5). ×1,000.
145. (p. 101): B. phlegmasiae uberis. *Kitt* (1899, original fig., p. 393). ×1,000.
146. (pp. 102, 134): Streptoc. lanceolatus. *Axelrad* (1903, original fig. 4). ×1,000.
147. (pp. 102, 134): B. coli. *Axelrad* (1903, original fig. 19). ×1,000.
148. (pp. 103, 153): B. bulgaricus. *Löhnis* and *Smith* (1916 *a*, original fig. 29). ×1,000.
149. (p. 103): Bac. aus Hackfleisch. *Maassen* (1904, original fig. XI, 4). ×1,000.
150. (pp. 103, 202): B. subtilis. *Hiss* and *Zinsser* (1911, original fig. 125).
151. (p. 104): B. Chauvoei. *Grassberger* (1903, original fig. 67). ×1,000.
152. (p. 104): Clostridium Pastorianum. *Winogradsky* (1902, original fig. 1). ×1,000.
153. (p. 105): B. leprae. *Kedrowski* (1910, original fig. 38 *a*). ×1,000.

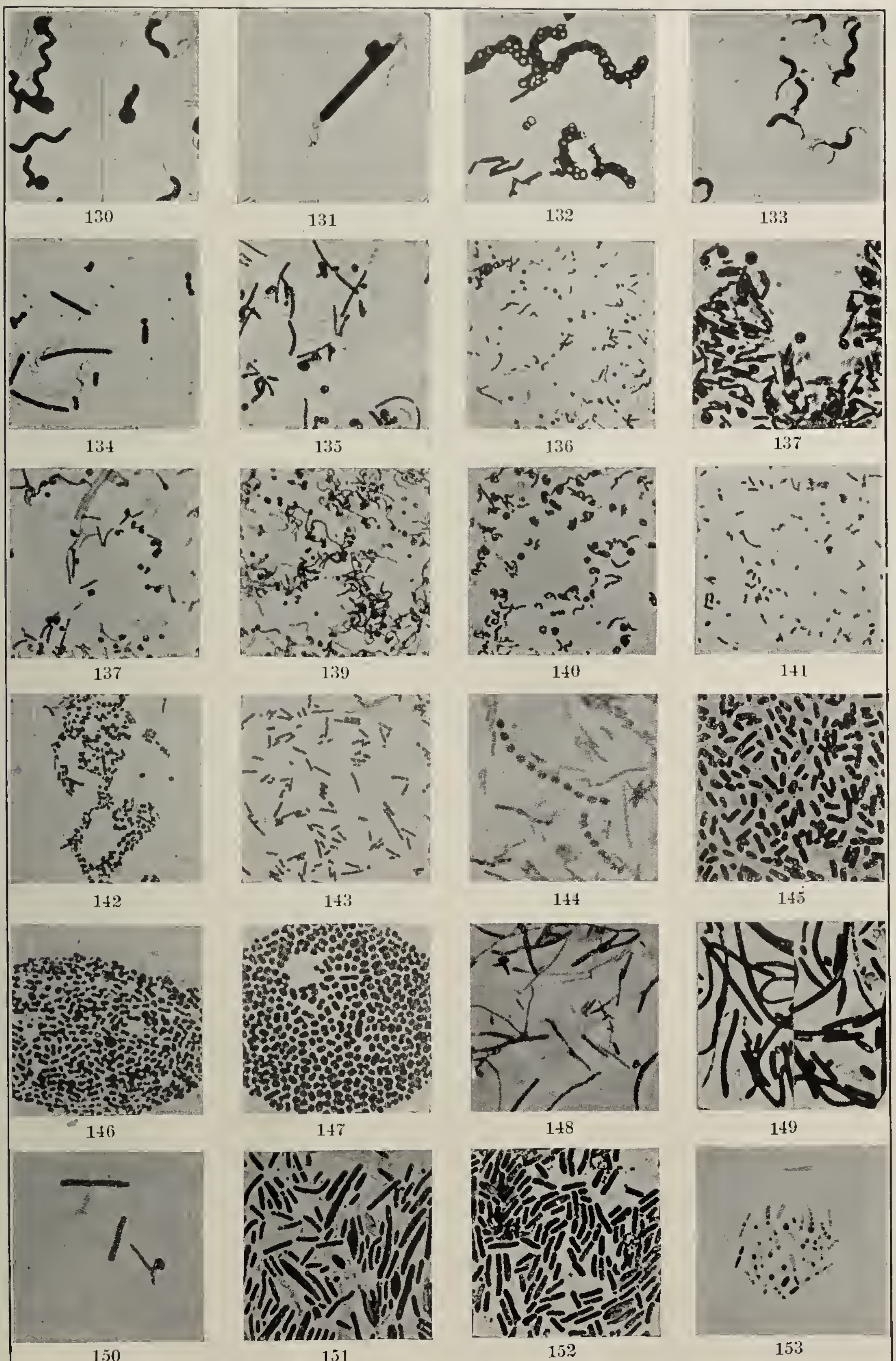
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PLATE XII.

Fig. 154. (pp. 105, 134): B. leprae. *Kedrowski* (1910, original fig. 38 *b*). ×1,000.
155. (pp. 105, 134): Meningitis. *Ghon, Mucha* und *Müller* (1906, original fig. 3). ×1,000.
156. (pp. 105, 134): Meningitis. *Ghon, Mucha* und *Müller* (1906, original fig. 18). ×1,000.
157. (pp. 105, 134): B. cyanogenes. *Neelsen* (1880, original fig. XI, 9). ×650.
158. (pp. 105, 134): V. cholerae. *Hammerl* (1906, original fig. 4). ×1,000.
159. (p. 106): B. fusiformis (?). *Rosenow* and *Tunnicliff* (1912, original fig. I, 3). ×750.
160. (p. 106): B. Azotobacter. *D. H. Jones* (1913, original fig. V, 9/10. ×1,000.
161. (p. 106): B. subtilis. *Marrassini* (1913, original fig. I, 28). ×1,000.
162. (p. 107): B. tuberculosis. *Meirowsky* (1914 *b*, original Pl. II *a*). ×2,000.
163. (p. 107): B. tuberculosis. *Meirowsky* (1914 *b*, original Pl. II *a*). ×2,000.
164. (pp. 107, 135): B. tuberculosis. *Meirowsky* (1914 *b*, original Pl. II *a*). ×2,000.
165. (p. 107): B. leprae. *Meirowsky* (1914 *b*, original Pl. II *b*). ×2,000.
166. (pp. 107, 135): B. leprae. *Meirowsky* (1914 *b*, original Pl. II *b*). ×2,000.
167. (pp. 107, 135): Spirillum rubrum. *Meirowsky* (1914 *b*, original Pl. V *a*). ×2,000.
168. (pp. 108, 151): M. candicans. *Löhnis* and *Smith* (1916 *b*, original fig. 31). ×1,000.
169. (pp. 108, 124): M. luteus. *Löhnis* and *Smith* (1916 *b*, original fig. 32). ×1,000.
170. (pp. 108, 132): Streptoc. lactis. *Löhnis* and *Smith* (1916 *b*, original fig. 30). ×1.000.
171. (pp. 108, 153): B. pneumoniae. *Löhnis* and *Smith* (1916 *b*, original fig. 37). ×1,000.
172. (pp. 108, 153): B. bulgaricus. *Löhnis* and *Smith* (1916 *b*, original fig. 36). ×1,000.
173. (p. 108): Azotob. Beijerinckii. *Löhnis* and *Smith* (1916 *b*, original fig. 33). ×1, 000.
174. (p. 108): B. fluorescens. *Löhnis* and *Smith* (1916 *b*, original fig. 28). ×1,000.
175. (p. 108): Az. vinelandii. *Löhnis* and *Smith* (1916 *a*, original fig. 24). ×1,000.
176. (pp. 108, 129): Az. chroococcum. *Löhnis* and *Smith* (1916 *b*, original fig. 26). ×1,000.
177. (p. 108): Bacillus sp. *Goadby* (1917, original fig. 14). ×1,000.

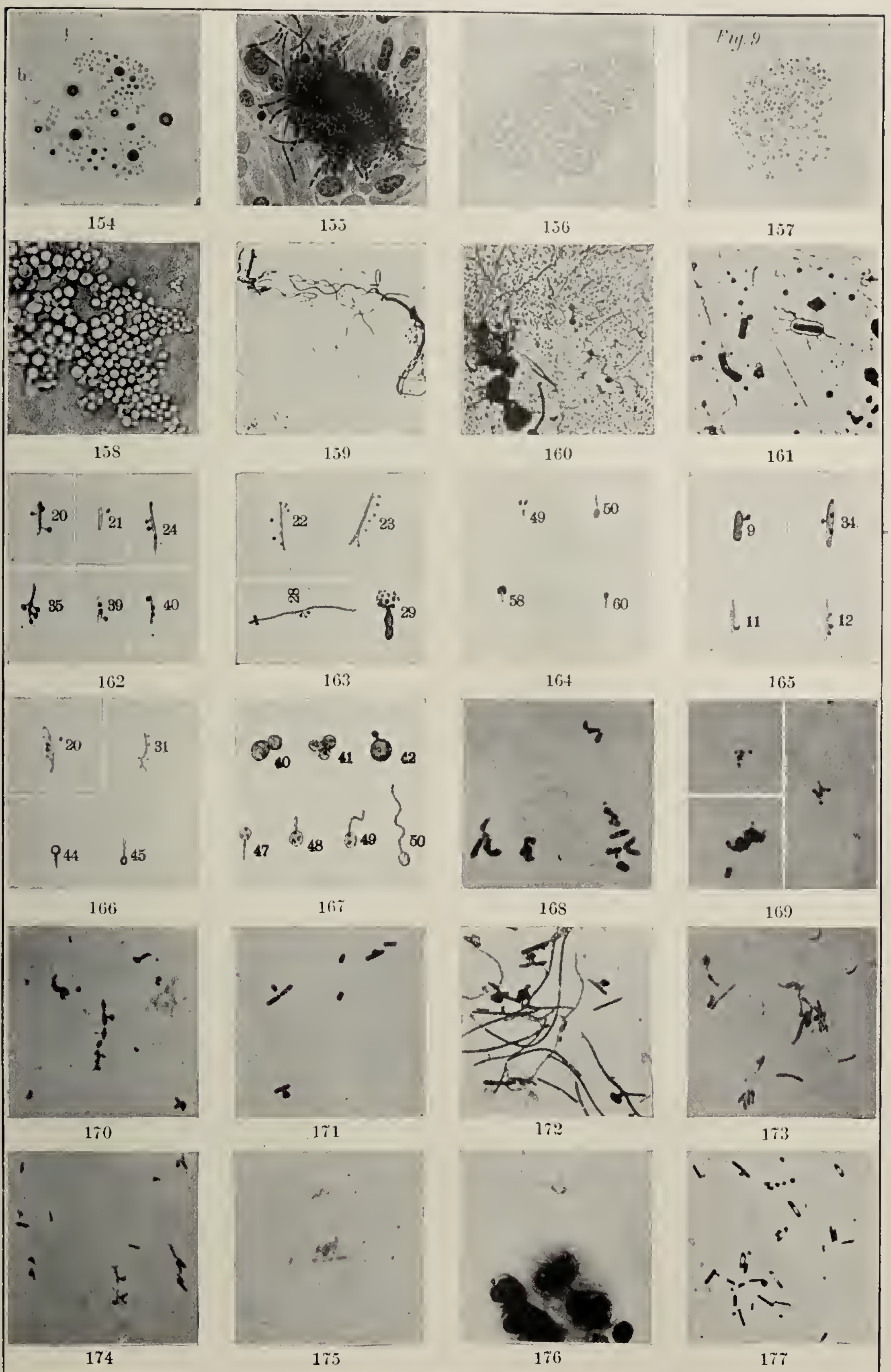
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PLATE XIII.

Fig. 178. (pp. 108, 192): B. paratyphi B. *Meirowsky* (1914 *b*, original Pl. III). ×2,000.
179. (pp. 108, 127): B. typhosus. *Hort* (1917 *a*, original fig. 1). × 1,500.
180. (pp. 108, 127): B. coli. *Hort* (1917 *a*, original fig. 2). × 1,500.

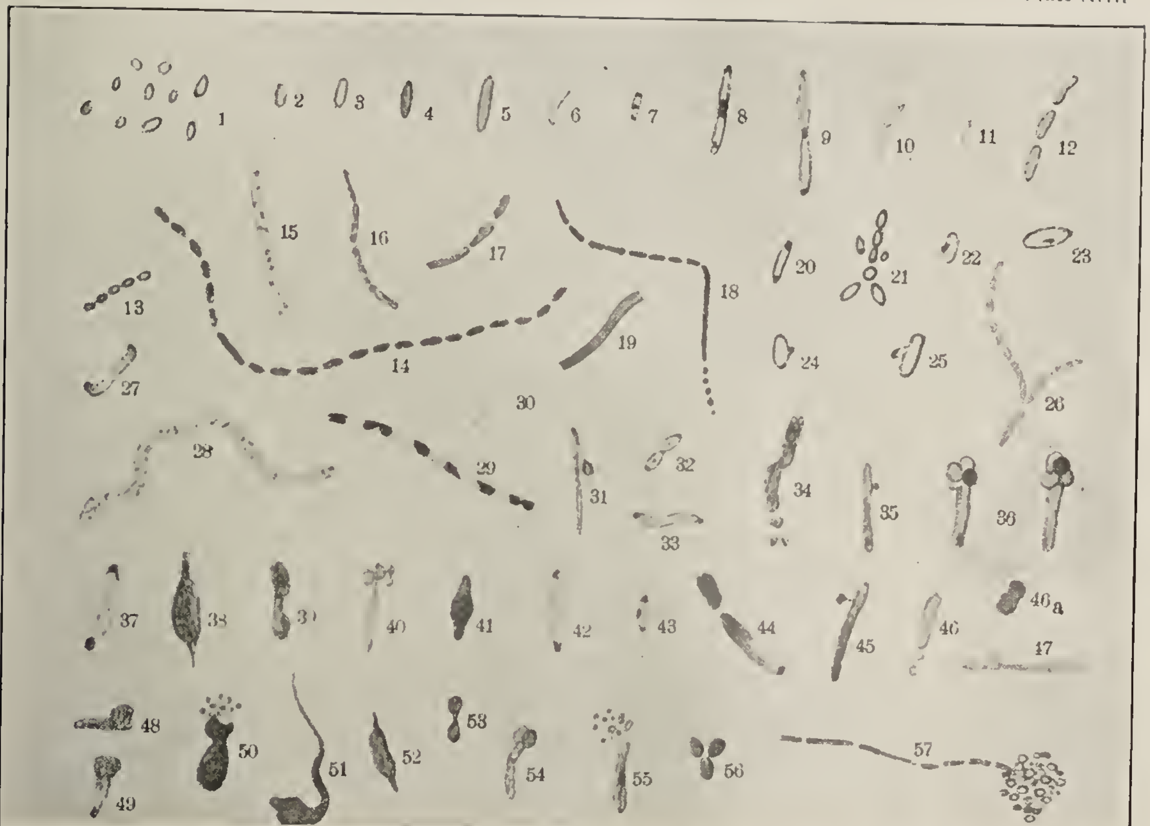
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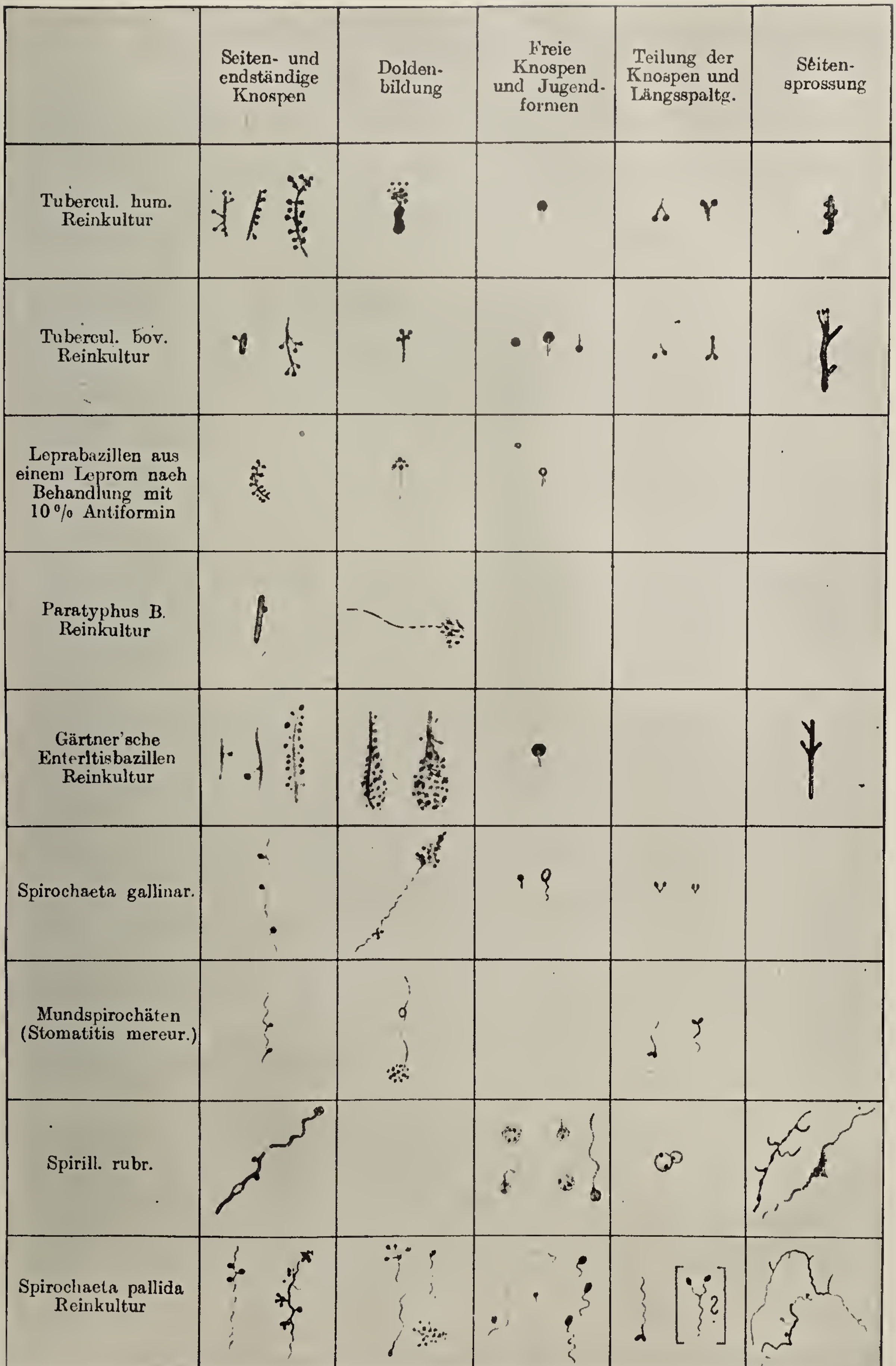
PLATE XIV.

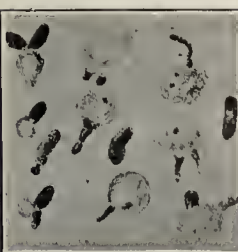
(pp. 107, 128, 158, 177): Budding and branching of bacteria. *Meirowsky* (1914 *b*, original Pl. XVIII). ×2,000.



Seiten- und endständige Knospen
Dolden-bildung
Freie Knospen und Jugend-formen
Teilung der Knospen und Längsspaltg.
Seiten-sprossung
Tubercul. hum. Reinkultur
Tubercul. bov. Reinkultur
Leprabazillen aus einem Leprom nach Behandlung mit 10 % Antiformin
Paratyphus B. Reinkultur
Gärtner'sche Enteritisbazillen Reinkultur
Spirochaeta gallinar.
Mundspirochäten (Stomatitis mercur.)
Spirill. rubr.
Spirochaeta pallida Reinkultur

PLATE XV.

FIG. 181. (p. 117): Plasmoptysis. *A. Fischer* (1906, original fig. III, 8). ×1,500.
182. (p. 124): B. coli. *Kellerman* and *Scales* (1916, original fig. 24). ×1,000.
183. (p. 124): Bac. no. 41. *Löhnis* and *Smith* (1916 *a*, original fig. 39). ×1,000.
184. (p. 128): Corynebacterium. *E. de Negri* (1916, original fig. 27) ×560.
185. (pp. 128, 202): B. coli. *Kellerman* and *Scales* (1916, original fig. 23). ×1,000.
186. (p. 128): B. Azotobacter. *Löhnis* and *Smith* (1916 *a*, original fig. 3). ×1,000.
187. (p. 128): B. Azotobacter. *Löhnis* and *Smith* (1916 *a*, original fig. 4). ×1,000.
188. (p. 128): *B.* Azotobacter. *Löhnis* and *Smith* (1916 *b*, original fig. 1). ×1,000.
189. (p. 126): Az. chroococcum. *Beijerinck* (1901 *b*, original fig. 4). ×1,000.
190. (p. 129): Az. vitreum. *Löhnis* and *Smith* (1916 *a*, original fig. 6). ×1,000.
191. (p. 127): B. Azotobacter. *Löhnis* and *Smith* (1916 *a*, original fig. 5). ×1,000.
192. (pp. 126, 194): "Phthisiogenic microbe." *Schroen* (1904, original fig. VIII). ×500.
193. (p. 129): B. Azotobacter. *Löhnis* and *Smith* (1916 *a*, original fig. 21). ×1,000.
194. (p. 132): "Syphilis Bacillus." *Niessen* (1898, original fig. 13). ×900.
195. (p. 132): B. radicicola. *Hilter* und *Störmer* (1903, original fig. II, 1). ×1,000.
196. (p. 132): B. radicicola. *Hilter* und *Störmer* (1903, original fig. II, 2). ×1,000.
197. (pp. 132, 136): B. subtilis. *Löhnis* and *Smith* (1916 *b*, original fig. 27). ×1,000.
198. (p. 135): Nitrosococcus. *Winogradsky* (1891, original fig. XVIII, 2). ×1,000.
199. (p. 135): B. coli. *Kellerman* and *Scales* (1916, original figs. 19 and 20). ×1,000.
200. (p. 135): B. coli. *Kellerman* and *Scales* (1916, original figs. 21 and 22). ×1,000.
201. (p. 135): V. cholerae. *Stamm* (1914, original fig. 20). ×1,000.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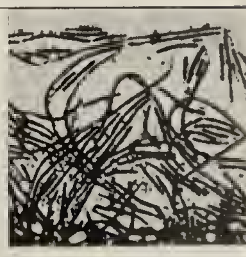
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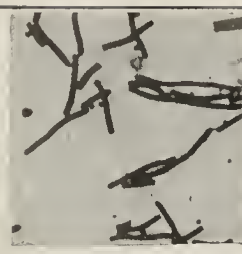
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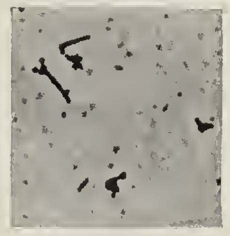
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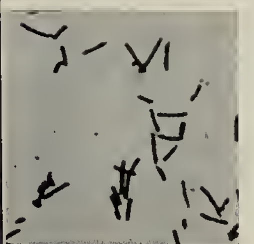
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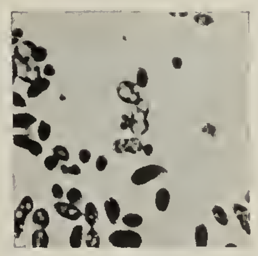
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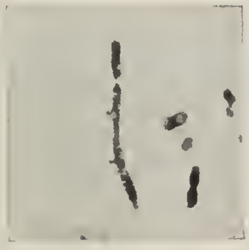
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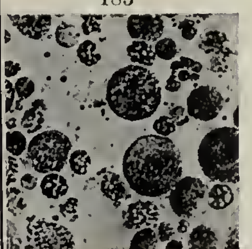
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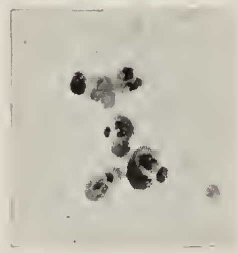
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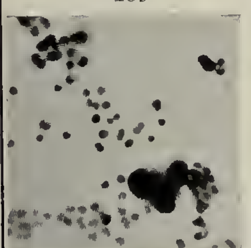
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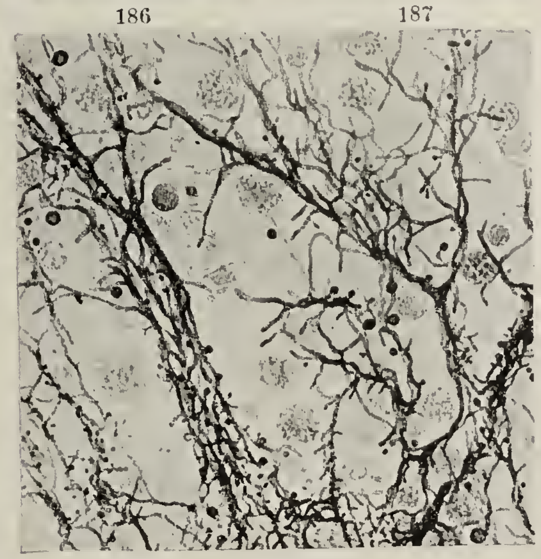
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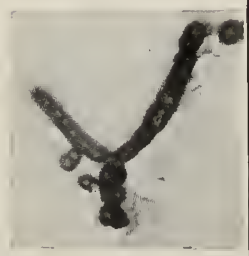
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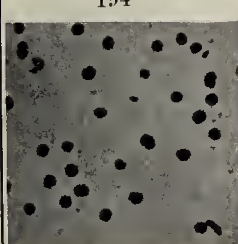
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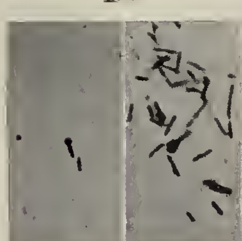
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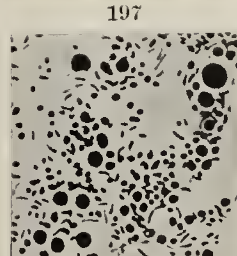
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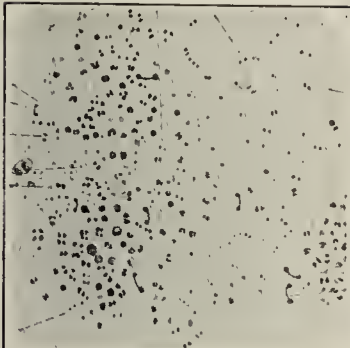
PLATE XVI.

Fig. 202. (p. 145): Microc. gonorrhoeae. *Herzog* (1913, original fig. III, 5). ×1,000.
203. (p. 149): Hematocyts. *Fokker* (1887, original fig. I, 1). ×770.
204. (p. 149): Bacilli from blood. *Fokker* (1888, original fig. III, 2). ×770.
205. (p. 168): Zoogloea with embryonal areas. *Bastian* (1905, original fig. 12). ×500.
206. (p. 168): Regeneration of cells. *Bastian* (1905, original fig. 11, B/C). ×500.
207. (p. 168): Zoogloea in transformation. *Bastian* (1905, original fig. 13). ×750.
208. (p. 168): Cell formation. *Bastian* (1907, original fig. 33). ×500.
209. (p. 170): Macroplasts of B. rubescens. *Lankester* (1876, original fig. III, 8, 9, 15, 20). ×1,100.



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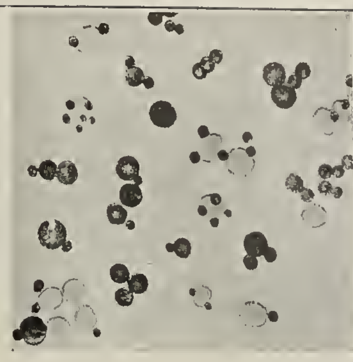

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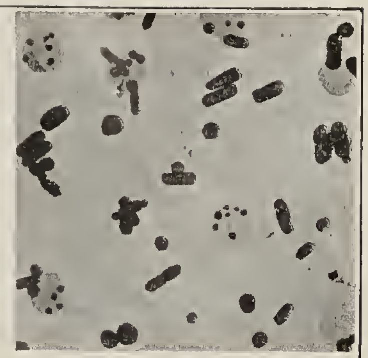

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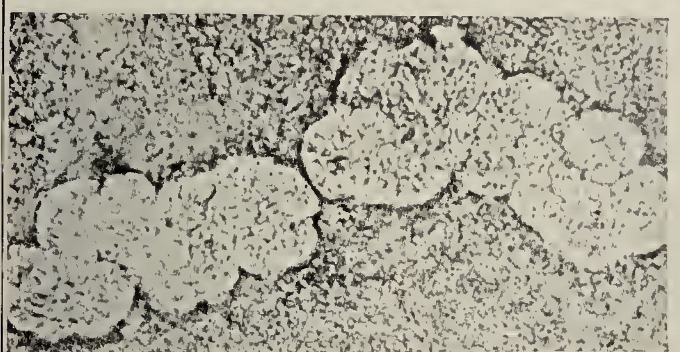

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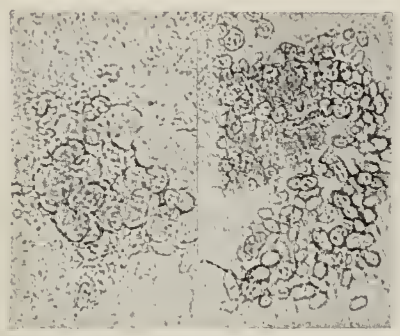

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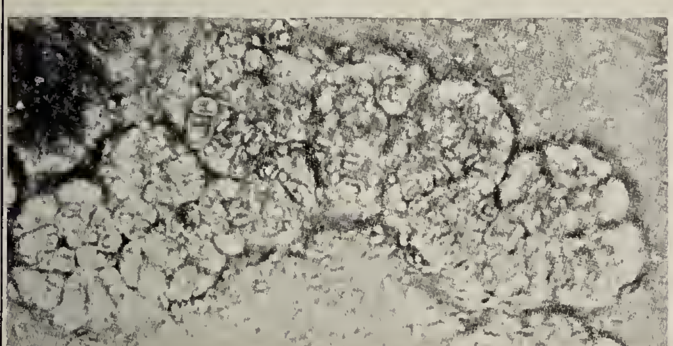

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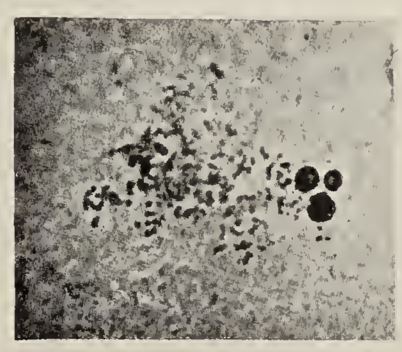

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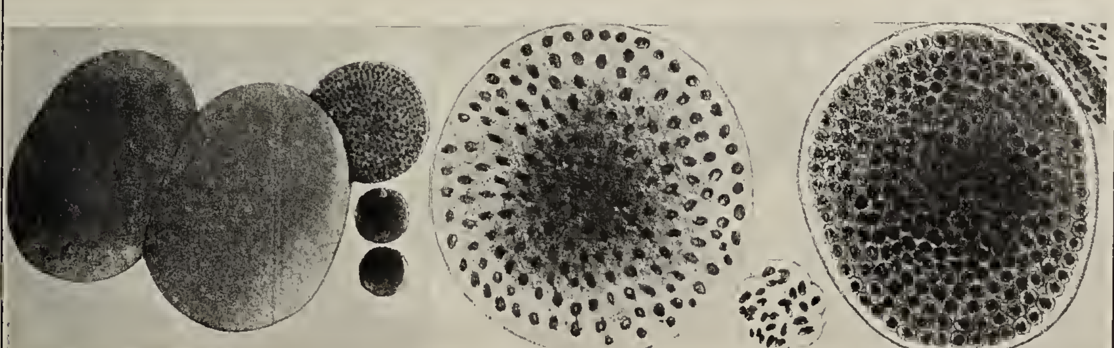

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PLATE XVII.

Fig. 210. (p. 169): Endocarditis. Klebs (1878, original fig. II, 3).

211. (p. 171): Septicaemia. *R. Koch* (1878, original fig. I, 8) .×700.

212. (p. 175): Plasmodia and filidia. *W. Winkler* (1899, original figs. 13, 15, 16, 34, 35, 40, 41, 48, 50). ×800–1,000.

213. (p. 176): Actinobacillosis. *Lignières* et *Spitz* (1902, original fig. 3 A and B).

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PLATE XVIII.

Fig. 214. (pp. 172, 191): Str. lactis. *Löhnis* and *Smith* (1916 *a*, original fig. 33). ×1,000.
215. (pp. 175, 191): Str. lactis. *Löhnis* and *Smith* (1916 *a*, original fig. 32). ×1,000.
216. (pp. 175, 190): M. candicans. *Löhnis* and *Smith* (1916 *b*, original fig. 56). ×1,000.
217. (pp. 175, 190): "Syphilis Bacillus." *Niessen* (1898, original fig. 13). ×900.
218. (p. 176): B. pestis. *N. K. Schultz* (1901 *a*, original fig. VII). ×1,000.
219. (p. 176): B. pestis. *N. K. Schultz* (1901 *a*, original fig. VIII). ×1,000.
220. (p. 176): B. pestis. *N. K. Schultz* (1901 *a*, original fig. IX). ×1,000.
221. (p. 176): B. pestis. *N. K. Schultz* (1901 *a*, original fig. XII). ×1,000.
222. (p. 176): Pasteuria ramosa. *Metchnikoff* (1888 *b*, original fig. III). ×850.
223. (pp. 177, 186): B. coli. *Kellerman* and *Scales* (1916, original fig. 29). ×1,000.
224. (pp. 177, 192): B. coli. *Kellerman* and *Scales* (1916, original fig. 7). ×1,000.
225. (pp. 178, 182): B. Azotobacter. *Löhnis* and *Smith* (1916 *a*, original fig. 9). ×1,000.
226. (pp. 178, 182): B. Azotobacter. *Löhnis* and *Smith* (1916 *a*, original fig. 7). ×1,000.
227. (pp. 178, 182): B. Azotobacter. *Löhnis* and *Smith* (1916 *b*, original fig. 41). ×1,000.
228. (pp. 178, 182): B. Azotobacter. *Löhnis* and *Smith* (1916 *a*, original fig. 8). ×1,000.
229. (pp. 178, 182): B. Azotobacter. *Löhnis* and *Smith* (1916 *a*, original fig. 11). ×1,000.
230. (pp. 178, 182): B. Azotobacter. *Löhnis* and *Smith* (1916 *b*, original fig. 43). ×1,000.
231. (pp. 178, 182): B. Azotobacter. *Löhnis* and *Smith* (1916 *a*, original fig. 12). ×1,000.
232. (p. 178): B. fluorescens. *Löhnis* and *Smith* (1916 *a*, original fig. 30). ×1,000.
233. (p. 178): B. subtilis. *Löhnis* and *Smith* (1916 *a*, original fig. 27). ×1,000.
234. (p. 184): B. fluorescens. *Löhnis* and *Smith* (1916 *a*, original fig. 42). ×1,000.
235. (p. 185): B. Azotobacter. *Löhnis* and *Smith* (1916 *a*, original fig. 17). ×1,000.
236. (p. 192): Alnus nodule. *Hiltner* und *Störmer* (1903, original fig. II, 8). ×1,000
237. (p. 179): Granulom. *E. de Negri* (1916, original fig. 62). ×560.

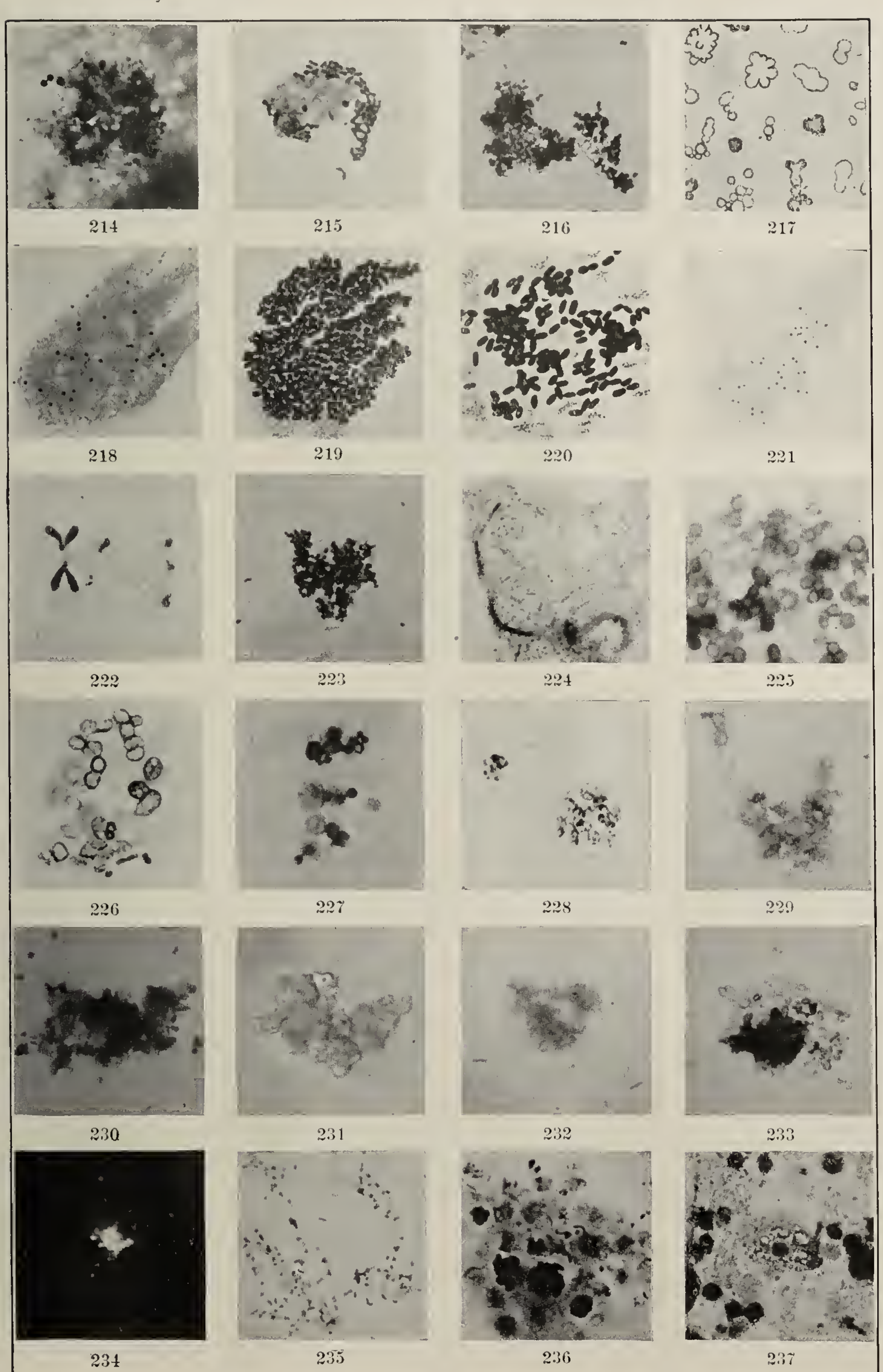
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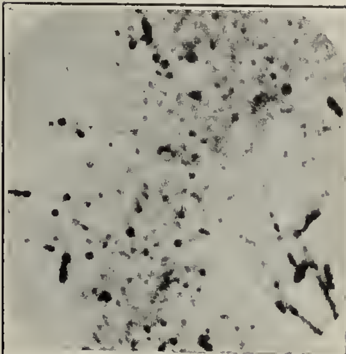
PLATE XIX.

FIG. 238. (pp. 176, 193): Ps. cerevisiae. *Fuhrmann* (1908, original. fig. I, 5). ×1,800.
239. (pp. 176, 181): B. erysipeloides. *Rosenbach* (1909, original fig. XIV, 6). ×970.
240. (pp. 176, 186): B. erysipeloides. *Rosenbach* (1909, original fig. XII, 2). ×970.
241. (p. 176): B. erysipeloides. *Rosenbach* (1909, original fig. XIII, 2). ×970.
242. (pp. 176, 181): B. erysipeloides. *Rosenbach* (1909, original fig. XII, 1). ×270.
243. (pp. 177, 187): B. typhi. *Almquist* (1916, original fig. 12). ×1,000.
244. (pp. 177, 193): V. cholerae. *Almquist* (1916, original fig. 22). ×1,000.
245. (pp. 177, 194): B. diphtheriae. *Almquist* (1917, original fig. 5). ×1,000.
246. (pp. 177, 192): B. acidi propionici c. *Almquist* (1917, original fig. 6). ×1,000.
247. (pp. 177, 184): Bact. antityphosum. *Almquist* (1917, original fig. 12). ×1,000.
248. (pp. 179, 184): Clumps from tonsils. *Mallory* and *Medlar* (1916, original fig. XX, 23). ×1,000.
249. (pp. 179, 194): Diphtheroids from lung. *Mellon* (1917, original fig. 5, pl. 2).



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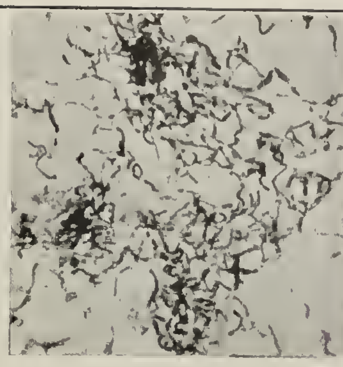

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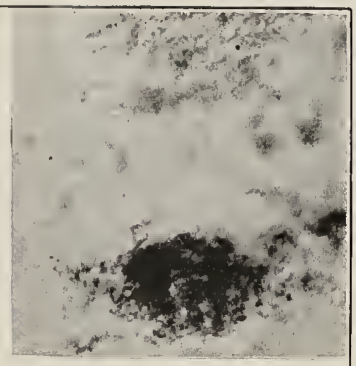

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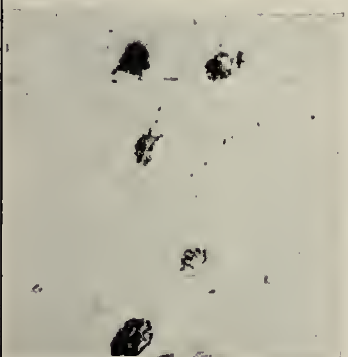

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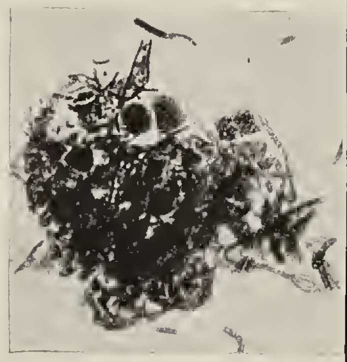

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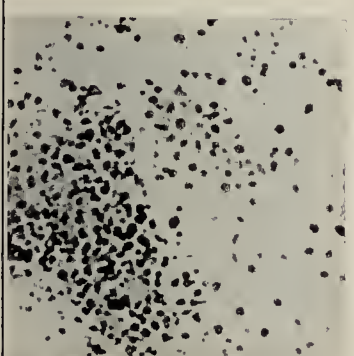

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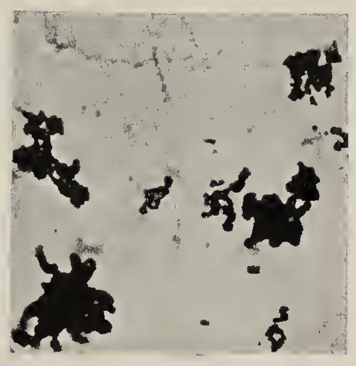

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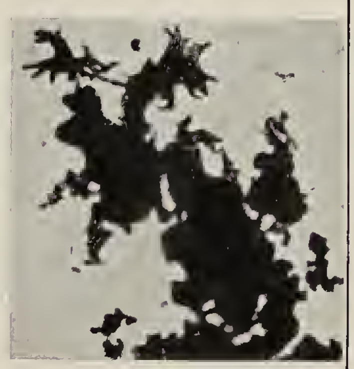

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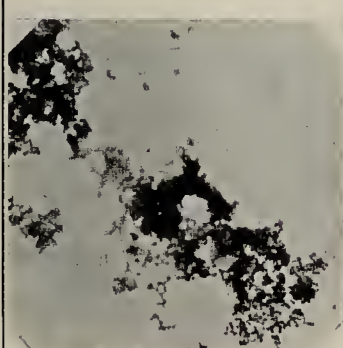

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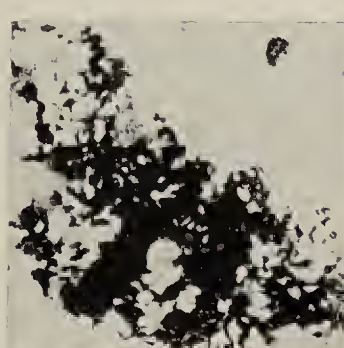

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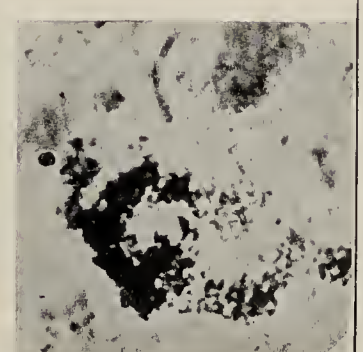

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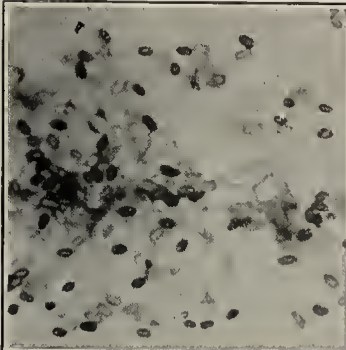
PLATE XX.

Fig. 250. (p. 178): B. Azotobacter. *Löhnis* and *Smith* (1916 *b*, original fig. 44). ×1,000.
251. (p. 178): B. Azotobacter. *Löhnis* and *Smith* (1916 *a*, original fig. 19). ×1,000.
252. (p. 178): B. Azotobacter. *Löhnis* and *Smith* (1916 *a*, original fig. 18). ×1,000.
253. (pp. 178, 185): B. Azotobacter. *Löhnis* and *Smith* (1916 *b*, original fig. 47). ×1,000.
254. (pp. 178, 185): B. Azotobacter. *Löhnis* and *Smith* (1916 *a*, original fig. 14). ×1,000.
255. (pp. 178, 185): B. Azotobacter. *Löhnis* and *Smith* (1916 *b*, original fig. 46). ×1,000.
256. (pp. 172, 185): B. Azotobacter. *Löhnis* and *Smith* (1916 *a*, original fig. 15). ×1,000.
257. (pp. 172, 185): B. Azotobacter. *Löhnis* and *Smith* (1916 *b*, original fig. 48). ×1,000.
258. (pp. 178, 185). B. Azotobacter. *Löhnis* and *Smith* (1916 *a*, original fig. 13). ×1,000.
259. (pp. 178, 185): B. fluorescens. *Löhnis* and *Smith* (1916 *b*, original fig. 49). ×1,000.
260. (pp. 178, 185): B. fluorescens. *Löhnis* and *Smith* (1916 *b*, original fig. 51). ×1,000.
261. (pp. 178, 185): B. fluorescens. *Löhnis* and *Smith* (1916 *b*, original fig. 50). ×1,000.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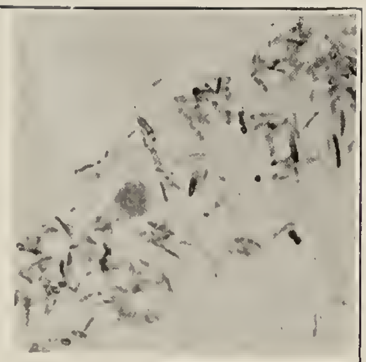
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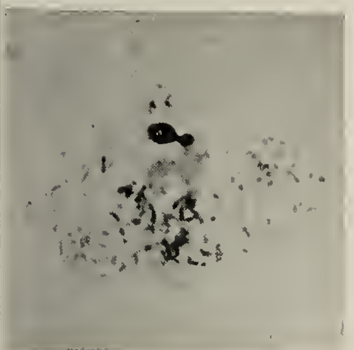
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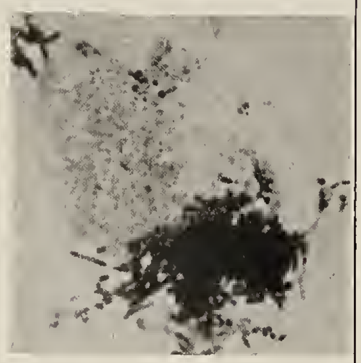
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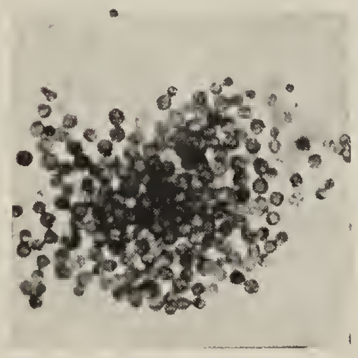
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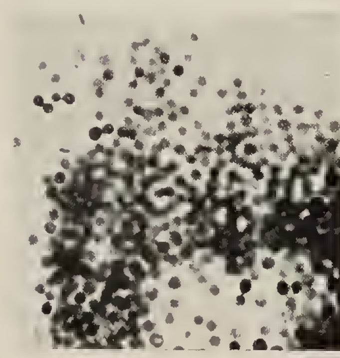
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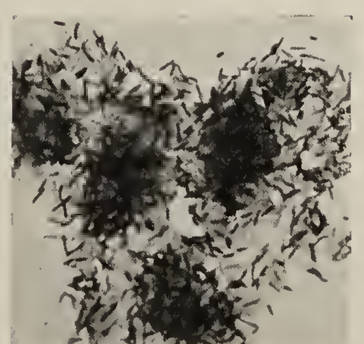
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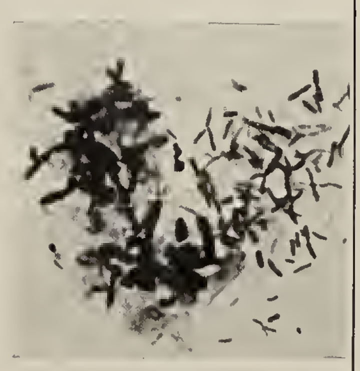
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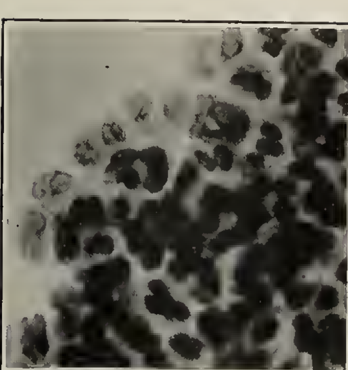
PLATE XXI.

FIG. 262. (pp. 178, 185): B. fluorescens. *Löhnis* and *Smith* (1916 *b*, original fig. 8). ×1,000.
263. (pp. 178, 185): B. fluorescens. *Löhnis* and *Smith* (1916 *b*, original fig. 63). ×1,000.
264. (pp. 178, 190): Sarcina flava. *Löhnis* and *Smith* (1916 *b*, original fig. 53). ×1,000.
265. (pp. 135, 193): Bact. acidulum. *Löhnis* and *Smith* (1916 *b*, original fig. 52). ×1,000.
266. (pp. 65, 193): B. malabarensis. *Löhnis* and *Smith* (1916 *b*, original fig. 4). ×1,000.
267. (pp. 174, 186): Yellow bacillus no. 41. *Löhnis* and *Smith* (1916 *a*, original fig. 28). ×1,000.
268. (p. 193): Nitrosomonas. *Omelianski* (1899, original fig. 2). ×1,000.
269. (p. 193): Nitrosomonas. *Winogradsky* (1892, original fig. 11). ×1,000.
270. (p. 193): Nitrosomonas. *Winogradsky* (1892, original fig. 15). ×1,000.
271. (p. 192): Clover nodule. *Hiltner* und *Störmer* (1903, original fig. II, 5). ×1,000.
272. (p. 192): Pea nodule. *Hiltner* und *Störmer* (1903, original fig. II, 6). ×1,000.
273. (p. 192): Clover nodule. *Löhnis* and *Smith* (1916 *a*, original fig. 34). ×1,000.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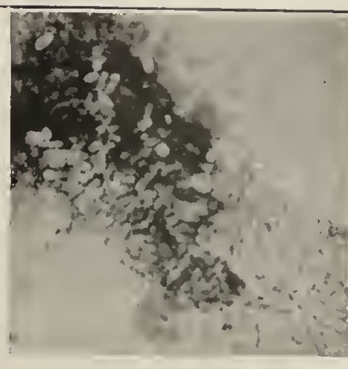
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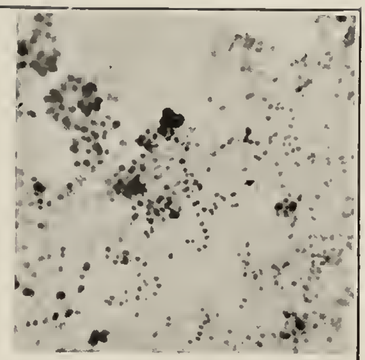
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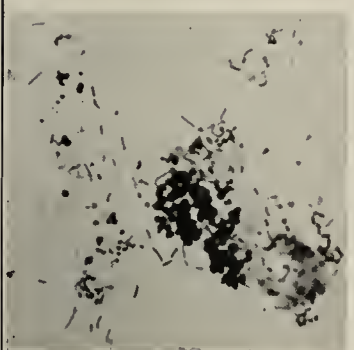
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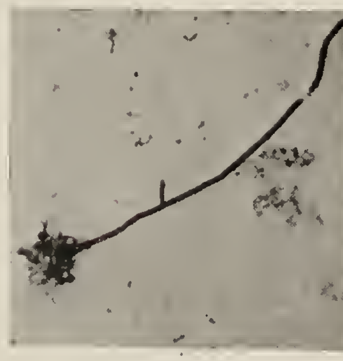
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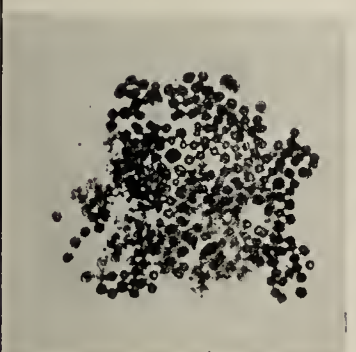
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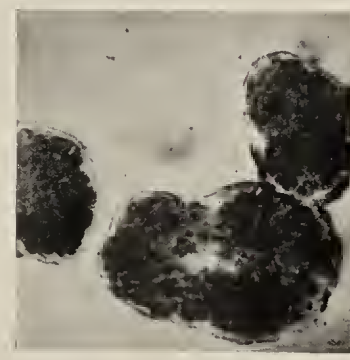
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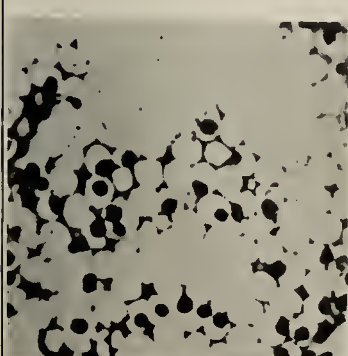
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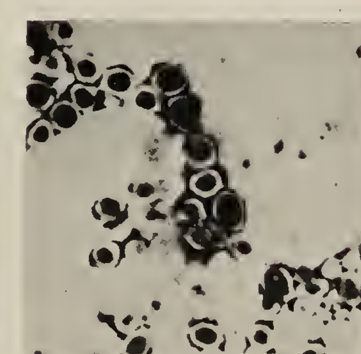
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PLATE XXII.

Fig. 274. (p. 186): Rosette formation. *M. Jones* (1905, original fig. 1). ×1,500.
275. (p. 190): Ascococcus Billrothii. *F. Cohn* (1875, original fig. V, 5). ×65.
276. (p. 190): M. botryogenus. *Rabe* (1886, original fig. IV, 2). ×100.
277. (p. 200): B. radiobacter. *Löhnis* and *Smith* (1916 *b*, original fig. 29). ×1,000.
278. (p. 197): Chromatium Okenii. *Foerster* (1892, original fig. 26). × 750.
279. (p. 197): B. Azotobacter. *Löhnis* and *Smith* (1916 *a*, original fig. 1). ×1,000.
280. (p. 197): B. Azotobacter. *Löhnis* and *Smith* (1916 *a*, original fig. 2). ×1,000.
281. (p. 197): B. Azotobacter. *Löhnis* and *Smith* (1916 *b*, original fig. 18). ×1,000.
282. (p. 197): B. Azotobacter. *Löhnis* and *Smith* (1916 *b*, original fig. 19). ×1,000.
283. (p. 197): B. Azotobacter. *Löhnis* and *Smith* (1916 *b*, original fig. 25). ×1,000.
284. (pp. 197, 204): B. Azotobacter. *Löhnis* and *Smith* (1916 *b*, original fig. 20). ×1,000.
285. (p. 197): B. fluorescens. *Löhnis* and *Smith* (1916 *b*, original fig. 23). ×1,000.

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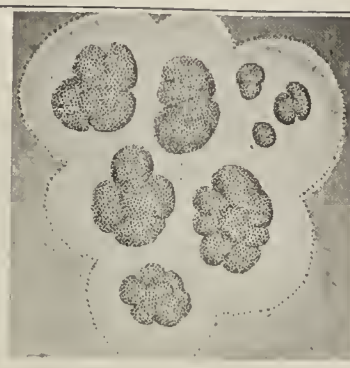

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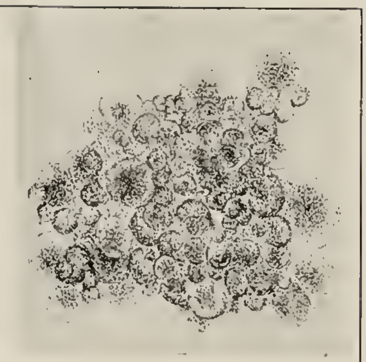

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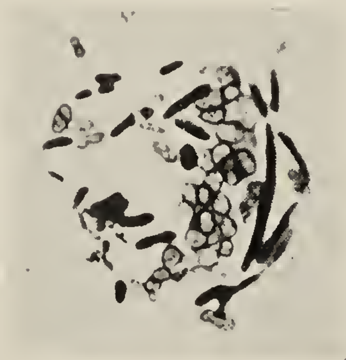

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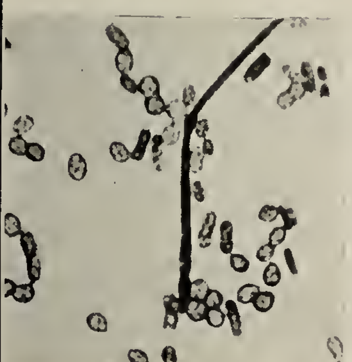

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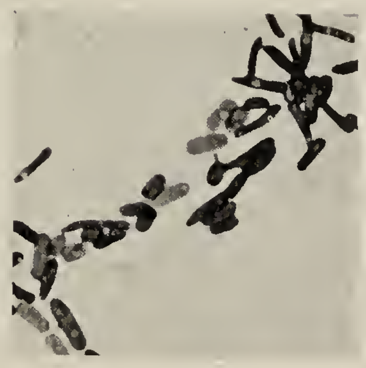

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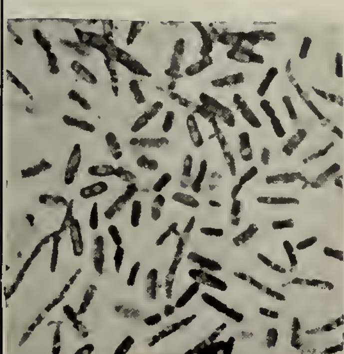

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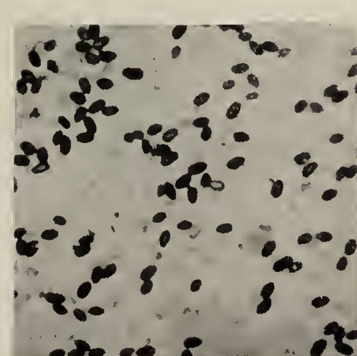

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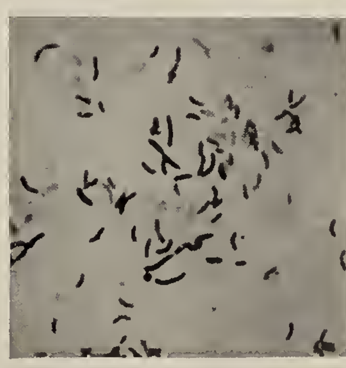

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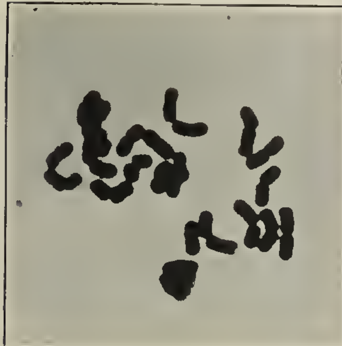
PLATE XXIII.

Fig. 286. (p. 197): B. subtilis. *Löhnis* and *Smith* (1916 *b*, original fig. 22). ×1,000.
287. (p. 197): B. subtilis. *Löhnis* and *Smith* (1916 *b*, original fig. 21). ×1,000.
288. (p. 197): B. Chauvoei. *Itzerott* und *Niemann* (1895, original fig. 48). ×1,000.
289. (p. 197): B. fluorescens. *Axelrad* (1903, original fig. 22). ×1,000.
290. (pp. 197, 201): Bact. esterificans. *Maassen* (1899, original fig. XI, 1). ×1,000.
291. (p. 197): Bacilli from [illegible]aw. *Günther* (1906, original fig. 8). ×1,000.
292. (pp. 197, 202): B. subtilis. *Hiss* and *Zinsser* (1914, original fig. 125).
293. (p. 197): B. subtilis. *Hiss* and *Zinsser* (1914, original fig. 125).
294. (p. 197): Azotob. chroococcum. *Walton* (1915, original fig. II, 8). ×1,000.
295. (p. 208): Azotobacter cells not heated. *Löhnis* and *Smith* (1916 *b*, original fig. 57). ×1,000.
296. (p. 208): Azotobacter cells heated. *Löhnis* and *Smith* (1916 *b*, original fig. 58). ×1,000.
297. (p. 211): Flake from agar. *Löhnis* and *Smith* (1916 *b*, original fig. 61). ×1,000.



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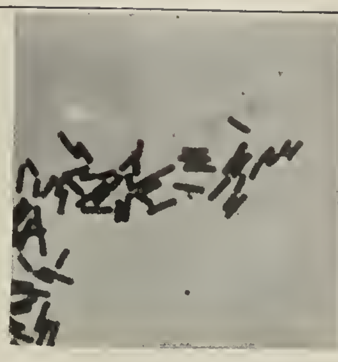

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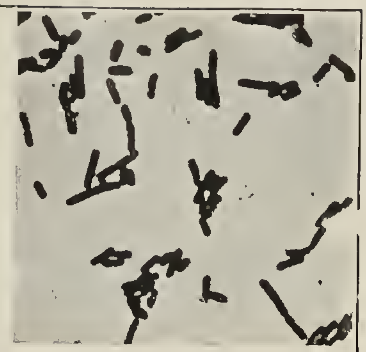

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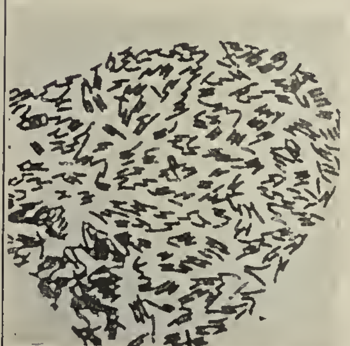

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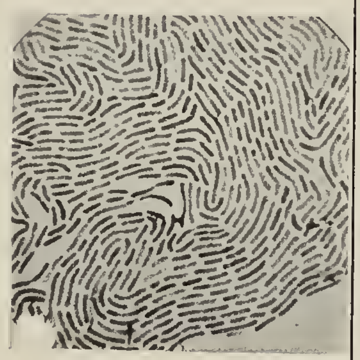

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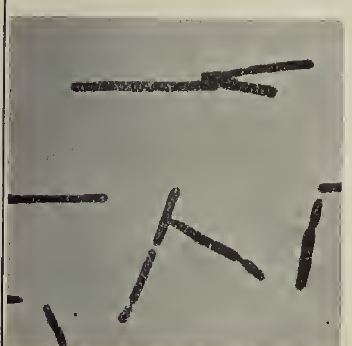

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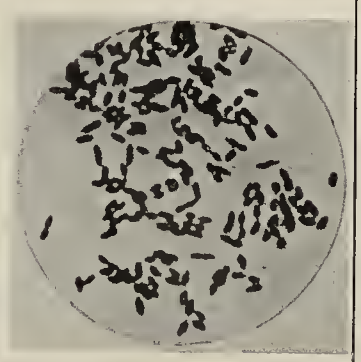

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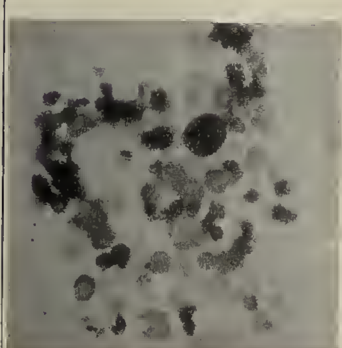

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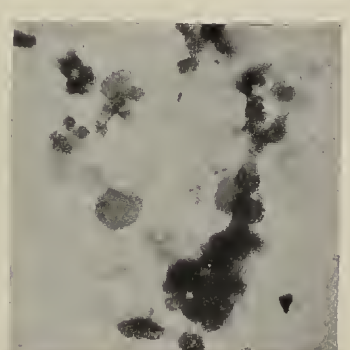

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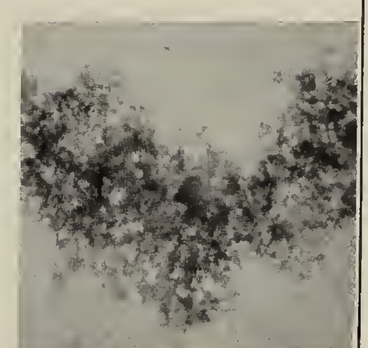

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